DRUG EMERGENT METABOLIC SYNDROME IN PATIENTS ON ANTIPSYCHOTIC MEDICATION

AKHIL ABHIJNHAN

Dissertation submitted to The Tamil Nadu Dr.MGR Medical University, in part fulfillment of the requirement for MD Branch XVIII Psychiatry Final Examination to be held in April 2015

CERTIFICATE

I hereby declare that this dissertation titled ‘Drug emergent metabolic syndrome in patients on antipsychotic medication’ is a bonafide piece of work done by Dr Akhil Abhijnhan at the Department of Psychiatry, Christian Medical College, Vellore. This work has not been submitted to any university in part or full.

Dr.Anna Tharyan
Professor and Head
Department of Psychiatry
Christian Medical College
Vellore 632002

CERTIFICATE

I hereby declare that this dissertation titled ‘Drug emergent metabolic syndrome in patients on antipsychotic medication’ is a bonafide piece of work done by Dr Akhil Abhijnhan under my guidance at the Department of Psychiatry, Christian Medical College, Vellore. This work has not been submitted to any university in part or full.

Dr.Deepa Ramaswamy
Professor of Psychiatry
Department of Psychiatry
Christian Medical College
Vellore

DECLARATION

I hereby declare that this dissertation titled 'Drug emergent metabolic syndrome in patients on antipsychotic medication' is a bonafide work done by me under my guidance of Dr. Deepa Ramaswamy, Professor of Psychiatry, Christian Medical College, Vellore. This work has not been submitted to any university in part or full.

Dr. Akhil Abhijnhan
PG Registrar
Department of Psychiatry
Christian Medical College
Vellore

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PG Registrar
Department of Psychiatry
Christian Medical College
Vellore 632 002

Sub: **Fluid Research grant project**:
Drug emergent metabolic syndrome in patients on antipsychotic medication.
Dr. Akhil Abhijnhan, PG Registrar, Psychiatry, Dr. Deepa Braganza, Dr. Ranjith Padoli, Psychiatry-Unit II.

Ref: IRB Min. No. 8444 [OBSERVE] dated 10.09.2013

Dear Dr. Akhil Abhijnhan,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Deepa Braganza, Psychiatry, CMC.

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Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Dear Dr. Akhil Abhijnhan,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Drug emergent metabolic syndrome in patients on antipsychotic medication." on September 10, 2013.

The Committees reviewed the following documents:

1. Format for IRB application
2. CV's of Drs. Akhil Abhijnhan, Deepa Braganza, Ranjith Padoli
3. Consent form in English & Tamil
4. Participation Information Sheet in English & Tamil
5. No of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on September 10, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Dr. Ashok Chacko	MD, DM, FRCP, FRCPG,FIMSA, FAMS	Director, Institute of Gastroenterology and Liver Disease, Madras Medical Mission, Chennai	External, Clinician

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report.** Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

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MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
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Fluid Grant Allocation:

A sum of 80,000/- INR (Rupees Eighty Thousand only) for 2 years. (A sum of Rs 40,000/- will be released for I st installment subsequent installment of 40,000/- each will be released at the end of the first year following the receipt of the interim progress report.)

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board
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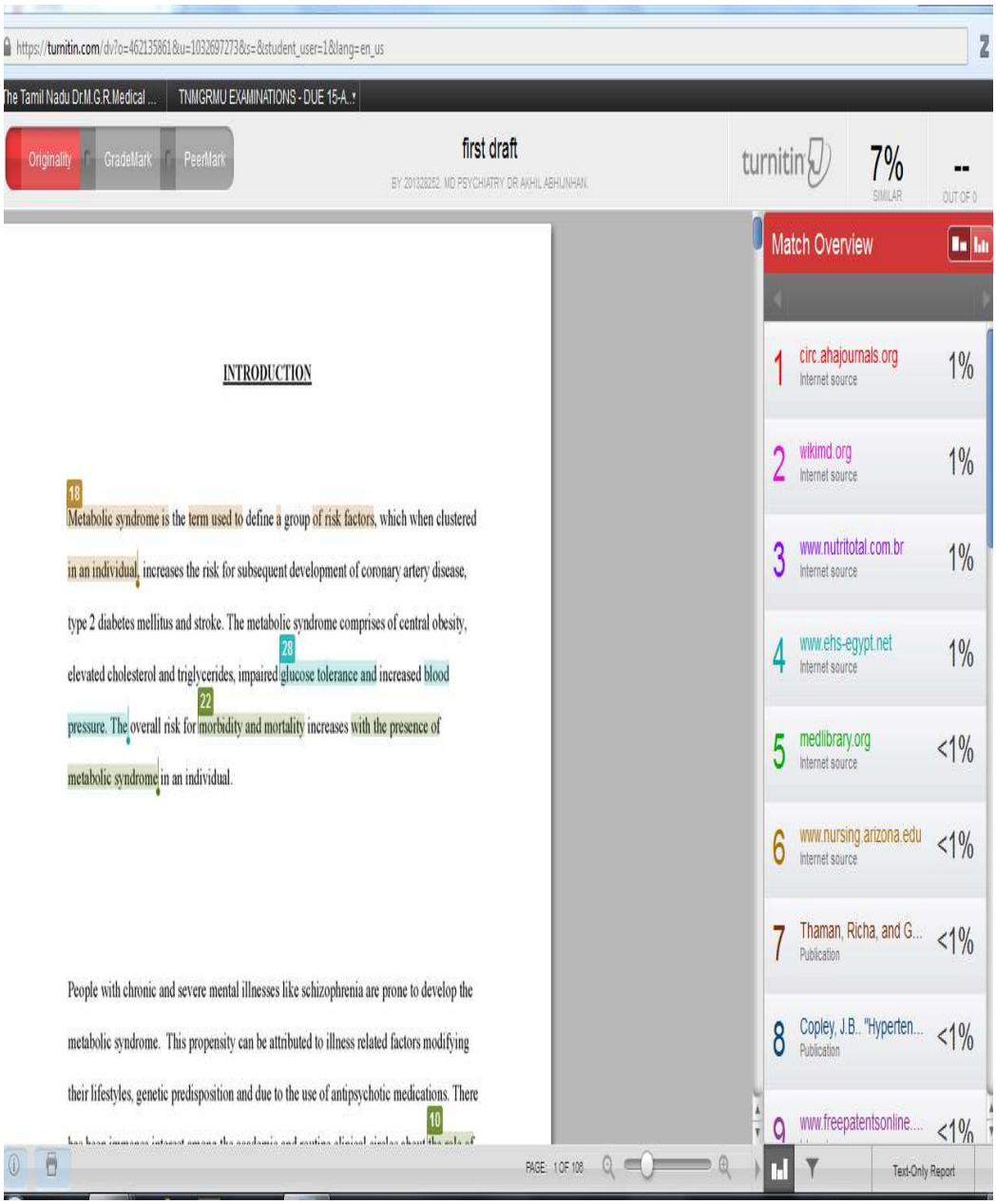
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INTRODUCTION
Metabolic syndrome is the term used to define a group of risk factors, which when clustered in an individual, increases the risk for subsequent development of coronary artery disease, type 2 diabetes mellitus and stroke. The metabolic syndrome comprises of central obesity, elevated cholesterol and triglycerides, impaired glucose tolerance and increased blood pressure. The overall risk for morbidity and mortality increases with the presence of metabolic syndrome in an individual.
People with chronic and severe mental illnesses like schizophrenia are prone to develop the metabolic syndrome. This propensity can be attributed to illness related factors modifying their lifestyles, genetic predisposition and due to the use of antipsychotic medications. There
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My parents and sister for all ways being there.

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Mrs.Priscilla who played a pivotal role during the recruitment phase of the study.

Most of all, to the patients and their relatives, without whose co-operation this study would not have been possible.

INDEX

ABSTRACT

TITLE OF THE THESIS:

Drug emergent metabolic syndrome in patients on antipsychotic medication

DEPARTMENT **:** Psychiatry

NAME OF THE CANDIDATE: Akhil Abhijnhan

DEGREE AND SUBJECT **:** MD Psychiatry

NAME OF THE GUIDE **:** Dr. Deepa Ramaswamy

OBJECTIVES (30 WORDS)**:**

This study aims to estimate the prevalence and incidence of metabolic syndrome in antipsychotic naive psychiatric population followed up over 3 months and to identify associated risk factors.

METHODS (100 WORDS)**:**

A prospective cohort study was conducted where the prevalence of metabolic syndrome in antipsychotic naive patients was measured at the time of recruitment. Those who did not fulfil the criteria for metabolic syndrome and required antipsychotic medications were followed up over a period of 3 months and reassessed for the incidence of metabolic syndrome. Participants fulfilling the inclusion and exclusion criteria were recruited from both outpatient and inpatient facilities in the department of Psychiatry, Christian Medical College-Vellore. Socio-demographic, anthropometric, blood pressure and blood parameters were recorded in addition to making note of other risk factors such as family history.

RESULTS (90 WORDS)**:**

Analysis of baseline characteristics was done using 148 participants. Prevalence of metabolic syndrome in antipsychotic naive patients with mental illness was 19% using National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition while it was 12% with International Diabetes Federation (IDF) criteria. Prevalence of sub-threshold metabolic syndrome was 40% when only 2 criteria and 74% when any one of the NCEP ATP III criteria were fulfilled. Three months later, analysis of the full data available for 14 participants gave incidence rate of 7% using NCEP ATP III definition.

KEYWORDS: metabolic syndrome, antipsychotic naive, NCEP ATP III, IDF

INTRODUCTION

Metabolic syndrome is the term used to define a group of risk factors, which when clustered in an individual, increases the risk for subsequent development of coronary artery disease, type 2 diabetes mellitus and stroke. The metabolic syndrome comprises of central obesity, elevated cholesterol and triglycerides, impaired glucose tolerance and increased blood pressure. The overall risk for morbidity and mortality increases with the presence of metabolic syndrome in an individual.

People with chronic and severe mental illnesses like schizophrenia are prone to develop the metabolic syndrome. This propensity can be attributed to illness related factors modifying their lifestyles, genetic predisposition and due to the use of antipsychotic medications. There has been immense interest among the academic and routine clinical circles about the role of antipsychotic medications in the pathogenesis of the metabolic syndrome. This has been of particular interest given the current clinical practice guidelines of a shift in the use of second generation antipsychotic medications as first line choice in psychiatric illness.

Numerous risk factors have been implicated in the development of metabolic syndrome. These include genetic vulnerability, lifestyle factors, poor diet habits, use of nicotine and alcohol, diabetes and chronic illnesses. The prevalence of metabolic syndrome is clearly high in people who have first degree relatives suffering from diabetes mellitus or dyslipidemia.

Prevention is one of the major armaments in the management of the metabolic syndrome as it ameliorates the risk of complications such as diabetes mellitus or cardiovascular events. The major preventive measures advocated are of weight reduction and regular physical exercise. Pharmacological interventions are recommended only when the above mentioned strategies fail. Overall pharmacological interventions have not been found to play a significant role in the management of metabolic syndrome.

The metabolic syndrome currently affects about a quarter of the world population. Distinct patterns in the prevalence of this syndrome have been identified with respect to high risk regions and ethnicities. Studies have also shown that there is a higher risk of metabolic syndrome in psychiatric populations on antipsychotic medications.

In this study we set out to identify antipsychotic naive patients who required treatment, evaluated their metabolic status, and followed them up over a period of three months to evaluate the development of metabolic syndrome. We also aimed to look at the possible factors which possibly influence or predict the development of metabolic syndrome is this specific subset of patients.

REVIEW OF LITERATURE

Metabolic Syndrome

Metabolic Syndrome signifies a collection of signs and symptoms, the presence of which is hypothesized to increase the risk of subsequent development of diabetes mellitus, stroke or coronary artery disease. On a broad perspective the major traits that are screened for are the presence of central obesity, dyslipidemia, impaired glucose tolerance and elevated blood pressure. As this syndrome has the propensity to increase an individual's risk of metabolic and coronary complications, it contributes significantly to the overall morbidity and mortality rates.

The historical roots to the origin of this syndrome can be traced back to the Italian physician and anatomist Morgnani who identified the association between episodes of what is now known as obstructive sleep apnoea and the presence of visceral obesity, elevated serum uric acid levels, hypertension and atherosclerosis. This syndrome as a separate entity that we understand today has bearing on the evolution of the clinical concepts of obesity and insulin resistance. In the 1920's various associations of risk factors for diabetes mellitus were hypothesised. A significant development in the 1940's was Harvard psychologist William Sheldon's theory of different somatotypes (ectomorph, endomorph and mesomorph) predisposing towards different temperaments, which was based on the differences in the distribution of adipose tissue on different parts of the body(1). In Marseilles in 1947, Dr Jean Vague made observations that upper body obesity (android obesity) predisposes to the development of atherosclerosis, calculi, diabetes and gout(2). According to him these findings were in stark contrast to the pattern of obesity he observed in women (gynoid obesity). Since he observed that these patterns were not exclusively limited to each gender, he even developed a formula called the "Index of Masculine Differentiation"

to quantitatively express the pattern. This was followed up in the 1960's by Avogaro and colleagues who made observations of frequent clustering of obesity, increased blood fat, diabetes mellitus and hypertension, and subsequent risk of coronary artery disease(3). The term "metabolic syndrome" was first used by Haller in 1977 when describing the additive effects of risk factors such as associations of diabetes mellitus, hepatic steatosis, hyperlipoproteinemia, hyperuricemia and obesity with atherosclerosis. In the same year Singer and colleagues used the same term for the association of cluster of obesity, gout, diabetes mellitus and hypertension with hyperlipoproteinemia.

This was however followed by a period of confusion in the 1980's when Jean Vague stated that visceral fat mass did not by itself contribute to the development of diabetes mellitus. A shift in the focus from obesity to the concept of insulin resistance was evident by the late 1980's and was highlighted by the seminal work of Gerald Reaven, who in his Banting Lecture to the American Diabetes Association in 1988 used the name Syndrome X to enumerate risk factors for the pathogenesis of coronary artery disease(4). These included disturbances of glucose and insulin metabolism, obesity, dyslipidaemia and hypertension. Reaven hypothesised that insensitivity to insulin leads to elevated levels of insulin in the blood which was the major aetiopathological mechanism. Ferranini and colleagues supported this theory and coined the term Insulin resistance syndrome(5). Norman Kaplan introduced the term "deadly quartet" to the occurrence of glucose intolerance, hypertension, hypertriglyceridemia and upper –body obesity wherein he melodramatically assigned the pathogenic role to the presence of hyperinsulinemia (6). Metabolic syndrome is also known by the term "Syndrome X Plus". This was an amalgamation of the elements of syndrome X

described by Reaven to additional elements of upper body obesity, physical inactivity and ageing(7).

PATHOPHYSIOLOGY

The current understanding is that of complex interactions between genetic and environmental factors underpinning the aetio-pathogenesis of the Metabolic Syndrome. These factors can be summarised:

Insulin resistance & Glucose intolerance

Central Obesity

Hypertension

Dyslipidaemia

Pro-inflammatory state

Prothrombotic state

Genetics

Insulin resistance & Glucose intolerance

Insulin resistance has been postulated to be one of the primary pathogenic mechanisms(8). Insulin is secreted by the pancreas. It's major function is as an anabolic hormone influencing the metabolism of proteins and lipids; transport of amino acid and ions, and inadvertently affecting the cell cycle (9). In Insulin resistance the target organs lose the ability to utilize insulin leading to increased insulin level in the blood.(10). The hyperinsulinemia compensates by maintaining normoglycemia but causes insulin hyperactivity in other target organs which is

hypothesised to lead to the development of metabolic syndrome(11). Insulin resistance has been postulated to be the result of defects at various sites including the receptor itself, the pre-receptor and post receptor. The anti-atherogenic property of insulin is affected in insulin resistance through phosphatidlyinositol-3kinase pathway impairment(9).

Abdominal adipose tissue deposits have been believed to have a central role in the development of insulin resistance. These abdominal stores are known to release non-esterified fatty acids into the blood through which they get over deposited in the liver and muscle. This leads to over activity of insulin and subsequent development of insulin resistance in these tissues. The insulin over activity leads to lipolysis in the fatty tissues through its stimulatory effect on lipoprotein lipase. As a result the level of free fatty acids increases. These free fatty acids produce toxic substances which further increase the insulin resistance, hence leading to a vicious cycle (12). Of all the fat stores, visceral fat is considered to be most detrimental(11). Hyper insulinemia also accelerates the production of very low density lipoproteins and thereby increasing the triglyceride levels and resultant hypertension(13).

Central Obesity

The role of central obesity in metabolic syndrome is evident from the stance taken by the IDF to use “central obesity syndrome” as a synonym(14). The central fat stores are considered to be more metabolically active that the peripheral reserves. Studies have proposed that the development of central obesity precedes that of other components of the metabolic syndrome and have emphasised weight reduction as the primary prevention strategy(15). Central obesity has also been incriminated in hypothesis related to development of lipotoxicity. The metabolic products released by

the visceral fat stores gain direct entry to the liver through the portal circulation. Thus free fatty acids accumulate in the liver, pancreas and the heart leading the respective organ dysfunctions. This has the cumulative effect of impaired regulation of blood cholesterol and insulin levels.

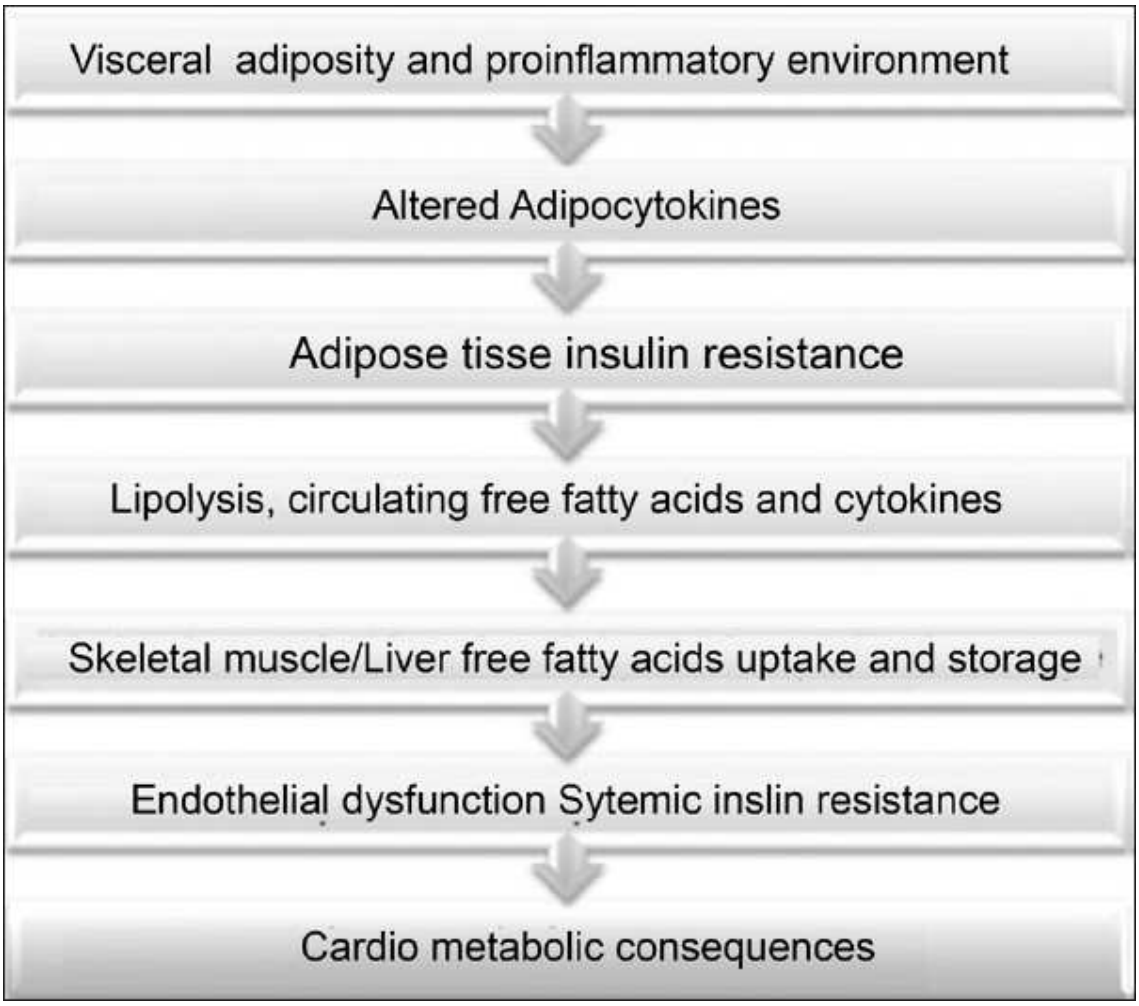
So based on the current understanding there can be two hypotheses:

1. Common Soil Theory: metabolic syndrome and central obesity are not causally linked but are common endpoints to shared genetic and environmental factors.

2. The visceral adipocytes are more metabolically active than their peripheral counterparts and hence enhanced lipolysis contributes towards elevated levels of free fatty acids in the plasma.

The metabolic products of the visceral adipocytes drain directly into the liver due to the anatomical advantage via the portal venous system (16)(17)

Pathophysiology of Central Obesity as cause for metabolic syndrome(17)



Hypertension

Hypertension is one of the key symptoms of the metabolic syndrome. All the components of the metabolic syndrome are hypothesized to influence the pathogenesis of hypertension. This is one of the elements of the metabolic syndrome which has a high tendency to go undetected. Hypertension has been most commonly associated with dyslipidaemia, glucose intolerance and obesity(18). Some authorities suppose that out of these factors, obesity maybe the strongest risk factor for uncontrolled hypertension. The Framingham Heart Study results highlighted that in 78% of men and 65% of women, excess weight was contributory towards developing hypertension(19). Insulin and leptin are two hormones which have been postulated to be further evidence of the strong correlation between obesity and hypertension. (20). Leptin is proposed to increase the blood pressure by sympathetic nervous system activation(21)

Another mechanism in the pathogenesis of hypertension is the activation of the Renin-Angiotensin System (RAS) by hyperglycemia and insulin with resultant elevation of Angiotensin, AT1 receptor and Angiotensin II in the context of insulin resistance (22)

Dyslipidaemia

In the metabolic syndrome, the major changes seen in the lipid profile are increase in triglyceride levels and a fall in the high density lipoprotein (HDL) cholesterol levels. As a result of insulin resistance the serum levels of insulin will be elevated. This would theoretically lead to the breakdown of free fatty acids into triglycerides.

Obesity is also associated with low levels of HDL. Elevated levels of triglycerides also contribute to reduction in the HDL levels. The reduction is not only in the

number but also in the size of individual HDL particles. The smaller HDL particles are less efficient in combating the process of atherogenesis.

The low density lipoproteins (LDL) generally maintain normal levels in the metabolic syndrome. They are however more denser and smaller which facilitate atherogenesis and increased risk of developing Ischemic Heart Disease (23).

Pro-inflammatory state

Metabolic syndrome has long been associated with chronic subclinical inflammation (12). More specifically insulin resistance and endothelial dysfunction have been found to be associated with low grade inflammation(24). It has also been hypothesised that the inflammatory cytokines released by adipose tissue lead to insulin resistance. Another model views metabolic syndrome and obesity as forms of stress which the body handles by activation of the inflammatory pathway. Proponents of this model have put forward the term “metaflammation” to signify metabolically triggered inflammation. Studies have shown positive association between obesity and C-reactive protein in women (25) . These findings have prompted researchers to argue for the inclusion of CRP as a criterion to diagnose metabolic syndrome (26).

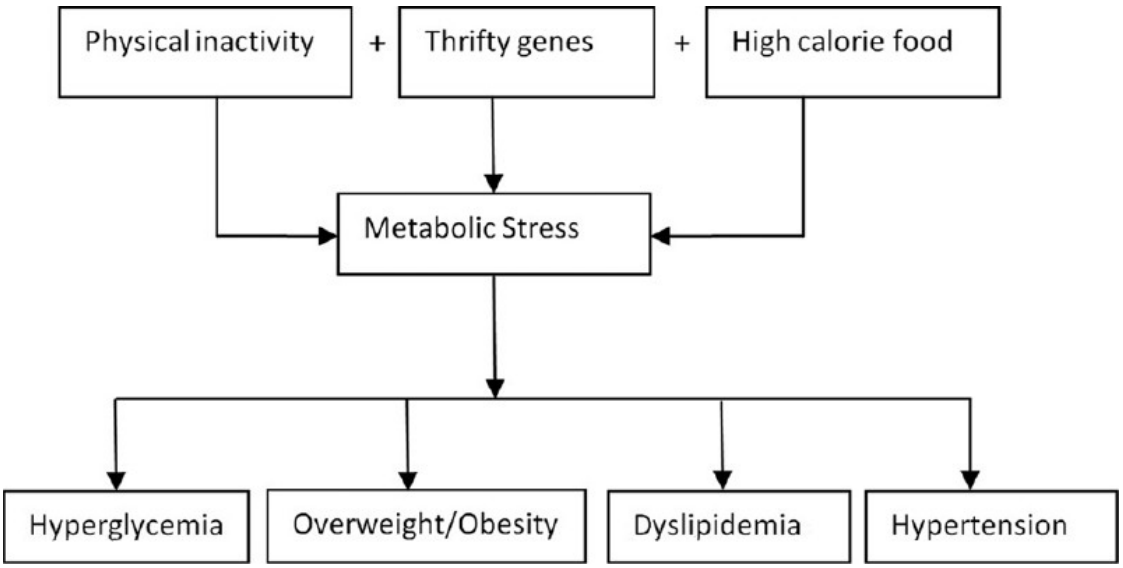
Prothrombotic state

Metabolic syndrome is characterised by elevated levels of plasma plasminogen activator inhibitor 1 (PAI-1) and fibrinogen. Like the CRP, fibrinogen is also an acute phase reactant. Hence in the metabolic syndrome, both prothrombotic and and proinflammatory phases might be interconnected(13). Studies have shown elevated levels of Thrombin Activatable Fibrinolysis Inhibitor (TAFI), CRP, IL6 and fibrinogen in metabolic syndrome. These 4 biomarkers have been proposed to be

included among the risk assessment for metabolic syndrome(27), though they are not currently included in any of the diagnostic guidelines.

Genetics

Current low power studies and the difference of opinions on the definition of metabolic syndrome have not facilitated in the identification of any strong candidates to propose genetic causality. Most of the proposed gene candidates are involved in energy storage functions and highlight the thrifty phenotype (28). It is hypothesized that when these genetic variants are exposed to an environment with high caloric diet in the absence of physical activity, they breakdown and form the phenotype with the dysfunction typical of the metabolic syndrome. Predominantly genes regulating thermogenesis and lipolysis are the prime candidates (29). Others include those working on adrenergic b-receptors (ADRB1, ADRB2 and ADRB3); insulin receptor substrates (IRS), tumor necrosis factor- alpha etc.



GENETIC FACTORS CONTRIBUTING TO METABOLIC SYNDROME(28)

Critique of Metabolic syndrome

The existence of the metabolic syndrome as a separate entity was questioned by a joint statement put forward by the American Diabetes Association and the European Association for the Study of Diabetes(30). The arguments were directed towards the lack of clarity of definition, multiple different phenotypes within the syndrome, lack of evidence base for setting up cut offs for the various components, inclusion in certain definitions of people with cardiovascular disease or diabetes and the non-inclusion of other risk factors (e.g. inflammatory markers) which may have equal or even greater contribution to the risk. The critical weakness of the current metabolic syndrome construct is that treatment of the syndrome is no different than treatment for each of its components.

This critique has been countered with the argument that focusing on central obesity as the pathogenesis behind metabolic syndrome takes out of the equation "other contributing risk factors" which fail to make it into the criteria for metabolic syndrome(31). Regarding the utility of metabolic syndrome, it has been highlighted that for mental health practitioners it is a less cumbersome method of calculating risk as opposed to using the Framingham score (32). Its utility as a construct which enables to label patients and initiate intensive intervention before the complications set in has also been emphasised on (33).

Definitions and Diagnosis

In the absence of concrete theories on the aetio-pathogenesis of metabolic syndrome, there are numerous definitions used to diagnose this syndrome. Guidelines provided by the WHO (World Health Organization), IDF (International Diabetes Federation)

and the revised National Cholesterol Education Program are the most widely employed ones. Each guideline reflects the predominant aetio-pathological model adopted.

World Health Organisation (WHO)

The WHO consultation group in 1998 gave a definition for metabolic syndrome along with a provisional classification of diabetes. This report was finalised by the WHO the following year and was published in their website(34). The primary outcome was the development of cardiovascular disease. Insulin resistance was defined as a prerequisite to diagnose the syndrome. This guideline also provided a set of criteria to identify insulin resistance. In addition to insulin resistance two other risk factors were required to complete the diagnosis.

Insulin resistance was defined as one of the following:

1. Type 2 diabetes
2. Impaired fasting glucose (IFG)
3. Impaired glucose tolerance (IGT)
4. Or for those with normal fasting glucose values (<110 mg/dL), a glucose uptake below the lowest quartile for background population under hyperinsulinemia, euglycemic conditions.

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
- HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women

- Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

Derived from Alberti et al(34).

One of the disadvantages of the WHO criteria is the need for special testing of blood glucose other than those used in routine clinical assessment.

EGIR (European Group for the Study of Insulin Resistance)

The European Group for the Study of Insulin Resistance in 1999 recognized the practical clinical difficulty in measuring insulin resistance in diabetic patients, while acknowledging that fasting insulin values were reliable measure of insulin resistance in non diabetic patients. The EGIR recommended that metabolic syndrome could be defined by the top 25% of the fasting insulin values among non-diabetic individuals AND two or more of the following:

- Central obesity: waist circumference ≥ 94 cm (male), ≥ 80 cm (female)
- Dyslipidemia: TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mmol/L or treated for dyslipidemia
- Fasting plasma glucose ≥ 6.1 mmol/L
- Hypertension: blood pressure ≥ 140/90 mmHg or antihypertensive medication

National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII)

The NCEP-ATP III was introduced in 2001. The primary clinical outcome for the metabolic syndrome according to the NCEP-ATPIII was identified as cardiovascular disease. Priority was placed on abdominal obesity. This was recognised by increase in the waist circumference which was listed as the first criterion. This clearly implied the emphasis laid on central obesity as the primary aetio-pathogenic factor in

metabolic syndrome. When 3 out of the 5 listed characteristics are present, a diagnosis of metabolic syndrome can be made:

1.Abdominal obesity, given as waist circumference	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
2.Triglycerides	≥150 mg/dL
3.HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
4.Blood pressure	≥130/≥85 mm Hg
5.Fasting glucose	≥110 mg/dL‡

After the publication of the NCEP ATP III, The American Diabetes Association established a new cut point of ≥100 mg/dL, above which persons have either prediabetes (impaired fasting glucose) or diabetes(35). This new cut point should be applicable for identifying the lower boundary to define an elevated glucose as one criterion for the metabolic syndrome.

The main advantage with the NATIONAL CHOLESTEROL EDUCATION PROGRAM-ADULT TREATMENT PANEL III criteria is that it is more user friendly. Moreover this guideline gives criteria which can be equally utilized in both clinical and research settings.

International Diabetes Federation (IDF)

The International Diabetes Federation introduced its diagnostic criteria in 2006. The primary clinical outcome targeted was both diabetes mellitus and cardiovascular disease. IDF places more importance on abdominal obesity in comparison to other components of metabolic syndrome. IDF introduced ethnic specific values for the measurement of waist circumference.

According to the IDF a diagnosis of metabolic syndrome can be made if the patient has:

1. Central obesity (defined as waist circumference[#] with ethnicity-specific values)

    - ≥ 94 cm in Europid men and ≥ 80 cm in Europid women
    - ≥ 90 cm in men and ≥ 80 cm in women from south and south east Asian, Japanese and ethnic south and central American origins

2. AND any two of the following:

- Raised triglycerides: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure (BP): systolic BP > 130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension

  Raised fasting plasma glucose (FPG): >100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetesIf FPG is >5.6 mmol/L or 100 mg/dL, an

oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome.

[#] If BMI is >30 kg/m², central obesity can be assumed and waist circumference does not need to be measured

American Association of Clinical Endocrinologists (AACE)

The American Association of Clinical Endocrinologists proposed a third set of criteria for the diagnosis insulin resistance syndrome.

RISK FACTOR		**COMPONENTS and CUT-POINTS FOR ABNORMALITY**
Overweight/obesity		BMI ≥25 kg/m2
Elevated triglycerides		≥150 mg/dL (1.69 mmol/L)
Low HDL cholesterol	Men	< 40 mg/dL (1.04 mmol/L)
	Women	< 50 mg/dL (1.29 mmol/L)
Elevated bloo□ pressure		≥130/85 mm Hg
2-Hour post glucose challenge		≥140 mg/dL
Fasting glucose		Between 110 and 126 mg/dL
Other risk factors		Family history of type 2 diabetes, hypertension, or CVD, Polycystic ovary syndrome, Sedentary lifestyle ,Advancing age, Ethnic□groups having high risk for diabetes/CVD

One of the problems though is that no defined number of risk factors is specified and diagnosis is left to clinical judgment.

COMPARISON OF THE 5 SETS OF DIAGNOSTIC CRITERIA

CRITERIA	WHO 1999	EGIR 1999	AACE 2003	NCEP ATP III 2005	IDF 2006
PREREQUISITE	Insulin resistance	Insulin resistance OR fasting hyperinsulinemia	Insulin resistance in the top 25%; glucose≥110 mg/dL; 2 hour glucose≥140 mg/dL		Waist≥ 94 cm in Europid men and ≥ 80 cm in Europid women
Number of criteria	Above & ≥2 of the below	Above & ≥2 of the below	Above & ≥2 of the below	≥3 of the below:	Above & ≥2 of the below
Waist circumference	waist: hip ratio >0.9 in men, >0.85 in women	≥ 94 cm (male), ≥ 80 cm (female)		>102 cm (male); > 88cm (female)	≥ 94 cm in Europid men and ≥ 80 cm in Europid women
Blood pressure	≥140 mm Hg systolic or ≥90mm Hg diastolic	≥ 140/90 mmHg or antihypertensive medication	≥130/85 mm Hg	≥130/≥85mm Hg	≥130/85 mm Hg

CRITERIA	WHO 1999	EGIR 1999	AACE 2003	NCEP ATP III 2005	IDF 2006
Fasting blood glucose		110-125 mg/dL	≥110 mg/dL; 2 hour glucose≥140 mg/dL	≥110 mg/dL Or on treatment for elevated blood glucose	≥110 mg/dL Or diagnosed diabetes
Triglycerides	≥150 mg/dL	≥ 2.0 mmol/L and/or or treated for dyslipidemia	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL
HDL cholesterol	<35 mg/dL in men or <39 mg/dL in women	< 1.0 mmol/L	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women

All of the five above mentioned are sets of criteria for defining the metabolic syndrome. Though similar conceptually, there are some significant disparities.

One of the major criticisms of the WHO criteria is the inclusion of diabetes mellitus as a criterion in diagnostic system intended for the identification of those at risk of developing diabetes mellitus. The need for doing the oral glucose tolerance test makes it impractical and expensive without any added benefit in diagnostic predictability.

Use of the NCEP criteria fails to identify those people on treatment for dyslipidemia or hypertension. It also suffers from the same problem as the WHO criteria with respect to the inclusion of diabetes mellitus as one of the criterion.

The IDF on the other hand takes into account treatment for hypertension and dyslipidemia in the criterions. It also provides ethnic specific values for the measurement of waist circumference. However, it too fails to exclude diabetes mellitus as a criterion.

ATP III metabolic syndrome criteria were updated in 2005(35,36). Updates included :

- Lowering the threshold for abnormal fasting glucose to 100 mg/dL
- Explicitly including diabetes in the hyperglycemia trait definition
- Explicitly including use of drugs for lipid control or blood pressure control in the dyslipidemia and hypertension trait definitions, respectively

Joint Interim Statement

Taking into account the various diagnostic criteria proposed by different organizations, a meeting between the major organizations was held in an attempt to unify the criteria(37). It was agreed that waist measurement would continue to be a useful preliminary screening tool. Three out of five would qualify a person for the metabolic syndrome. A single set of cut points would be used for all components except for waist circumference.

Joint Interim Statement Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic _130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol. *It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available. †The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose _-3 fatty acid presumes high triglycerides. ‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.(37)

Prevalence of metabolic syndrome in the general population

The prevalence of metabolic syndrome worldwide ranges from as high as 24% in the United States of America to as low as 8% in India (12). One study showed that the variation in the prevalence rates in women can range from 7% in France to 43% in Iran(12). There is also an age related increase in the prevalence of metabolic syndrome in both men and women in the USA.

An assessment by the International Diabetes Federation found that 25 % of the world's population has metabolic syndrome. Studies have shown that there is variability in the prevalence rates based on gender, racial and ethnic differences(19).

Prevalence of the metabolic syndrome according to the ATP III definition

Country	Age group (years)	Reference	Prevalence (%) Men	Prevalence (%) Women
India	>20	Gupta et al (38)	7.9	17.5
India	20–75	Deepa et al (39)	36.4[a]	46.5[a]
Iran	>20	Azizi et al	24	42
Mexico	20–69	Aguilar-Salinas et al (40)	Total = 26.6	
Oman	>20	Al-Lawati et al (41)	19.5	23.0
Finland	42–60	Laaksonen et al	13.7	—
Ireland	50–69	Villegas et al	21.8	21.5
Scotland	45–64	Sattar et al	26.2	—
Turkey	>31	Onat et al	27.0	38.6
Australia	>24	Unpublished data	19.5	17.2
Mauritius	>24	Cameron et al (41)	10.6[a]	14.7[a]
France	30–64	Balkau et al	10	7
United States (Native Americans)	45–49	Resnick et al	43.6	56.7
United States (Filipina Americans)	50–69	Araneta et al	—	34.3
United States	>19	Ford et al	24.2	23.5
United States	30–79	Meigs et al	26.9	21.4
United States (Non-Hispanic white)	30–79	Meigs et al	24.7	21.3
United States (Mexican American)	30–79	Meigs et al	29.0	32.8

a- Obesity criteria adjusted to waist circumference appropriate for an Indian population.

Prevalence of the metabolic syndrome according to the WHO definition

Country	Age group (years)	Reference	Prevalence (%) Men	Prevalence (%) Women
Australia	>35	Unpublished data	25.2	16.7
Denmark	60	Balkau et al	38.0	22.0
England	40–65	Balkau et al	>44.8	>33.9
England	40–75	Balkau et al	>12.6	>13.3
France	30–65	Balkau et al	>23.5	>9.6
France	35–64	Marques-Vidal et al	23.0	12.0
Italy	22–73 M, 22–55 F	Balkau et al	>12.2	>5.1
Italy	40–81 M, 40–55 F	Balkau et al	34.5	18.0
Netherlands	20–60	Balkau et al	>19.2	>7.6
Spain	35–64	Balkau et al	>25.5	>19.9
Sweden	46–68	Balkau et al	43.3	26.3
Mauritius	>24	Cameron et al	20.9	17.6
Occupied Palestinian Territories	30–65	Abdul-Rahim et al	Total = 17	
Ireland	50–69	Villegas et al	24.6	17.8
United States	40–74	Ford et al	41.3	32.7
United States	30–79	Meigs et al	30.3	18.1
United States (non-Hispanic white)	30–79	Meigs et al	24.7	17.2
United States (Mexican American)	30–79	Meigs et al	32.0	28.3

Abbreviations: F, female; M, male.

A “greater than” sign (>) means that the figure is an underestimate because one or more components of the metabolic syndrome were not measured.

Prevalence of the metabolic syndrome according to the EGIR definition

Country	Age group (years)	Reference	Prevalence (%) Men	Prevalence (%) Women
India	>20	Deepa et al	12.9	9.9
Finland	42–60	Laaksonen et al	21.1	–
Australia	>24	Unpublished data	18.6	13.3
Denmark	60	Balkau et al	22.0	16.0
England	40–65	Balkau et al	17.9	14.3
England	40–75	Balkau et al	4.7	3.9
France	30–65	Balkau et al	16.4	10.0
Italy	22–73 M, 22–55 F	Balkau et al	8.7	1.7
Italy	40–81 M, 40–55 F	Balkau et al	24.6	14.0
Netherlands	20–60	Balkau et al	13.3	8.3
Spain	35–64	Balkau et al	16.0	15.4
Sweden	46–68	Balkau et al	23.6	13.9
Mauritius	>24	Cameron et al	9.0	10.2

Prevalence of metabolic syndrome (MetS) in people with schizophrenia(42)

Study	Country	N	Design	Mean age	% MetS	Criteria
Heiskanen et al (78)	Finland	35		44.5	37.1	ATP III
Almeras et al (62)	Canada	42	Olanzapine	31.7	33.0	ATP III
	Canada	45	Risperidone	28.4	11.0	
Basu et al (65)	USA	33	Schizoaffective disorder	44.5	42.4	ATP III
Cohn et al (68)	Canada	240		42.7	44.6	ATP III
Kato et al (80)	USA	48		40.3	63.0	ATP III
Straker et al (96)	USA	89		39.8	29.2	ATP III
Meyer et al (83)	USA	1231		42.8	35.8	ATP III
McEvoy et al (82)	USA	342	White males	39.8	40.9	ATP III
		92	White females	44.2	56.2	ATP III
Saari et al (88)	Finland	31		31.0	19.4	ATP III
Correll et al (69)	USA	367		42.9	37.3	ATP III
De Hert et al (71)	Belgium	430		36.5	32.3	ATP III-A
De Hert et al (72)	Belgium	415		37.7	33.3	IDF
		100	First episode (maximal duration 2 year illness)	25.7	17.0	IDF
		130	Duration illness <10 years	29.0	28.5	IDF

Study	Country	N	Design	Mean age	% MetS	Criteria
		106	Duration illness 10 to 20 years	39.0	42.4	IDF
		79	Duration illness >20 years	49.8	49.4	IDF
Hagg et al (77)	Sweden	269		46.0	34.6	ATP III
Lamberti et al (81)	USA	93	Clozapine	34.4	53.8	ATP III
Srisurapanont et al	Thailand	38		53.7	36.2	ATP III
(95)		44		44.3	31.8	ATP III-A
Suvisaari et al (97)	Finland	108		34.6	34.0	ATP III-A
Teixeira and Rocha	Brazil	122	First episode, before treatment with FGA	23.1	5.7	ATP III-A
(98)		122	First episode, 3 year FGA	26.8	13.1	ATP III-A
Cerit et al (67)	Turkey	108	First episode, before treatment with SGA	21.9	5.6	ATP III-A
De Hert et al (74)	Belgium	108	First episode, 3 year SGA	25.1	31.6	ATP III-A
		2270		41.0	33.9	ATP III-A
De Hert et al (75)	Europe	58		36.3	40.0	ATP III-A
Ellingrod et al (76)	USA	99	First episode after treatment	26.1	18.2	IDF

Incidence of metabolic (MetS) in people with schizophrenia(42)

Study	Country	N	Design	Mean age	% MetS	Criteria
De Hert et al (71)	Belgium	31	Baseline aripiprazole	36.7	61.3	ATP III-A
			Endpoint aripiprazole	36.7	29.0	ATP III-A
Attux et al (64)	Brazil	44	First episode 6 months	26.3	6.8	ATP III
De Hert et al (73)	Belgium	155	After 3 months SGA	33.7	18.7	ATP III-A
		16	After 3 months amisulpride	33.7	6.3	ATP III-A
		16	After 3 months aripiprazole	33.7	0.0	ATP III-A
		20	After 3 months clozapine	33.7	45.0	ATP III-A
		45	After 3 months olanzapine	33.7	24.4	ATP III-A
		21	After 3 months quetiapine	33.7	19.1	ATP III-A
		37	After 3 months risperidone	33.7	10.8	ATP III-A
'Italien et al (79)	USA	91	Placebo trials, placebo	41.4	14.3	ATP III
		151	Placebo trials, aripiprazole	40.7	5.3	ATP III
		212	Active comparator trials, Olanzapine	37.7	27.4	ATP III
		198	Active comparator trials, Aripiprazole	37.6	15.7	ATP III

Study	Country	N	Design	Mean age	% MetS	Criteria
Saddichha et al (89)	India	30	First episode 6 weeks	26.9	27.5	IDF
Srisurapanont et al (95)	Thailand	35	Naturalistic 1 year follow-up	34.7	20.0	IDF
De Hert et al (74)	Belgium	122	First episode, 3 year FGA	26.8	9.8	ATP III-A
		108	First episode, 3 year SGA	25.1	27.8	ATP III-A
		8	First episode, 3 year Amisulpride	25.1	12.5	ATP III-A
		10	First episode, 3 year Aripiprazole	25.1	0.0	ATP III-A
		12	First episode, 3 year clozapine	25.1	50.0	ATP III-A
		34	First episode, 3 year Olanzapine	25.1	41.3	ATP III-A
		24	First episode, 3 year quetiapine	25.1	12.6	ATP III-A
		20	First episode, 3 year Risperidone	25.1	10.2	ATP III-A
Meyer et al (84)	USA	164	Baseline olanzapine	40.9	34.8	ATP III-A
			After 3 months olanzapine	40.9	43.9	ATP III-A
		147	Baseline risperidone	40.9	30.6	ATP III-A
			After 3 months risperidone	40.9	30.6	ATP III-A
		143	Baseline quetiapine	40.9	37.8	ATP III-A

Study	Country	N	Design	Mean age	% MetS	Criteria
			After 3 months quetiapine	40.9	37.1	ATP III-A
		77	Baseline ziprasidone	40.9	37.7	ATP III-A
			After 3 months ziprasidone	40.9	29.9	ATP III-A
		129	Baseline perphenazine	40.9	37.2	ATP III-A
			After 3 months perphenazine	40.9	38.0	ATP III-A
Schorr et al (93)	Netherlands	260	12 months incidence	41.0	14.0	ATP III
			12 months reversibility	37.0	33.0	ATP III

Management of Metabolic Syndrome

Since the prevalence of metabolic syndrome is as high as 25% of the world population, methods to effectively manage this syndrome should take a priority. As part of good clinical practise, prevention of metabolic syndrome should be targeted. The first step in prevention would be the identification of risk factors for metabolic syndrome (18). The prevention strategies should include diet modifications, lifestyle changes, weight loss and judicious use of pharmacological agents.(19)

Educational interventions should be based on client centred approach where the focus should be on eliciting the patient's knowledge of the syndrome and the understanding of the role of physical exercise and diet in its management. Effective treatment should include helping the patient set short term and long term targets and aid in providing consistent motivation to attain these set goals. Pharmacological strategies

should be resorted to only when the non-pharmacological strategies fail (19).

Numerous studies have emphasised on the role of weight reduction strategies. General recommendations are to target weight loss of at least 10% during the initial six months to a year. Weight reduction strategies need to continue until the BMI is less than 25(9).

The pharmacological strategies recommended in weight reduction are mainly based on two modes of action:

- Appetite suppressants
- Inhibitors of nutritional absorption

Appetite suppressants: Sibutramin and phentermine derivatives reduce appetite in the afternoon and evening if administered early in the morning.

Nutritional Absorption Inhibitor: Orlistat is found to reduce fat absorption by 30 %. It is recommended for use as a single agent at a time (20).

The success of weight loss programs is based on the inclusion of regular exercise in the program. Daily regular exercise has been shown to independently reduce the risk factors for metabolic syndrome (12).

Metabolic Syndrome and Mental Illness

The life expectancy of people with chronic and severe mental illnesses like schizophrenia is lower than the general population(43–46). In addition to this the mortality rates are two to three times higher than the general population. Moreover, over the past decades the mortality gap has been widening (47). In people with severe mental illness the risk of dying secondary to a cardiovascular event is nearly twice that of the general population (30–34).

Awareness about the high rates of morbidity and mortality among people with severe mental illness has led in the recent decades to alarm bells ringing about the nature of physical co-morbidities in severely mentally ill populations(48–50). Though the presence of multiple physical co-morbidities is of significance, another factor contributing to the morbidity and mortality rates is the poor access to good quality health care (51).

The risk factors for metabolic syndrome can also be attributed to the poor diet, sedentary habits and lifestyle prevalent among people with mental illness. There has also been an increasing awareness among clinicians about the contribution of antipsychotic medications in the incidence of metabolic syndrome (48–50). The changes in the metabolic profile of patients have been linked to the dose of the antipsychotic agent as well (52).

Studies on the prevalence of metabolic syndrome

Study	Country	Methodology	Sample Size	Criteria For Mets	Prevalence In drug Naive patients (%)	Comments
Grover et al (53)	India	Cross sectional study on patients with schizophrenia without any controls	46	IDF ATP III	10 (IDF) 13 (ATP III)	No controls
Pallava et al(54)	India	Cross sectional comparative study on 50 anti psychotic naive and 50 anti psychotic treated patients	50	IDF	26.0	10 patients had received anti psychotics in the past
Patel et al(55)	USA	52 weeks follow up of patients with early psychosis using double blind, flexible dose, multisite design	400	ATP III	4.31	Incidence of metabolic syndrome one year post treatment was 13.4%
Padmavati et al(56)	India	Never treated patients with chronic schizophrenia versus healthy controls	51	IDF	3.8	Prevalence of metabolic syndrome 7.8% in controls
De Hert et al(42)	Belgium	First cohort: retrospective chart review of 1st episode schizophrenia at baseline and after 3 years of FGA	148	ATP III	4.7	Prevalence of metabolic syndrome 13.1% after 3 years
		Second cohort: prospective naturalistic follow up study of 1st episode schizophrenia at baseline and after 3 yrs of SGA	148	ATP III	5.4	Prevalence of metabolic syndrome 30.6% after 3 years

Study	Country	Methodology	Sample Size	Criteria For Mets	Prevalence In drug Naive patients (%)	Comments
Saddich a et al (57)	India	Drug naive 1st episode schizophrenia followed up over 6 weeks on Olanzapine or Risperidone using double blind design	30	IDF	3.3	Prevalence of metabolic syndrome 31.8% after 6 weeks treatment
FGA-first generation antipsychotic, SGA- second generation antipsychotic, IDF- International Diabetes Federation, ATP III-Adult Treatment Panel III, MetS-Metabolic syndrome						

In the general population, metabolic syndrome is a strong predictor of diabetes mellitus, cardiovascular disease and mortality(58).

The concept of metabolic syndrome has become well recognized in the psychiatric circles. This has subsequently led to increasing the awareness in the mind of the clinical psychiatrist on the importance of screening for metabolic risk factors in patients being treated with antipsychotic medications(59,60).

Relationship between second generation antipsychotic medications and metabolic abnormalities(61–63)

DRUG	WEIGHT GAIN	RISK FOR TYPE 2 DIABETES MELLITUS	WORSENING LIPID PROFILE
CLOZAPINE	+++	+++	+++
OLANZAPINE	+++	+++	+++
RISPERIDONE	++	++/+	+
QUETIAPINE	++	++	++/+
ARIPIPRAZOLE*	+/-	+/-	+
ZIPRASIDONE*	+/-	+	+
AMISULPRIDE*	+/-	-	-
PALIPERIDONE*	+	+	+
ASENAPINE*	++/+	+	D
ILOPERIDONE*	++/+	+	D
BIFEPRUNOX*	+/-	+/-	D
Abbreviations- + : increased effect; - :no effect; D: discrepant results;*: newer drugs with limited long term data.			

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial one third of the patients met the NCEP criteria for metabolic syndrome at baseline

(64,65). Of them 88% had dyslipidemia, 62% had hypertension and 38% had diabetes mellitus while not on treatment(65) . There is significant difference between individual antipsychotic agents effects on weight, lipids and glucose metabolism (65,66)

The commonly implicated causal factors for metabolic syndrome in Schizophrenia are those of lifestyle related factors, psychotic illness related factors and antipsychotic medication related factors. A new entrant to this group are the possible genetic causes for metabolic syndrome in this particular subgroup(60,64). Points emphasising this causality are the presence of evidence of increased liability for the development of metabolic syndrome in patients with schizophrenia even before the institution of antipsychotic medications and the increased risk among first degree relatives to develop diabetes mellitus (67). Studies have also shown elevated levels of cortisol and blood sugars along with visceral adiposity even before the commencement of therapy with antipsychotic agents(66,68). One study highlighted a higher vulnerability in schizoaffective disorder as compared to schizophrenia or bipolar disorder for developing metabolic syndrome (69).

Metabolic Syndrome and Antipsychotic medications

Antipsychotic medications are attributed a major causal role in the incidence of metabolic syndrome in the mentally ill population. Though all antipsychotic medications have potential to cause weight gain, there is variable difference in the propensity to cause weight gain that is clinically relevant (>7% increase) (70). Associations between the receptor profile of antipsychotic agents and their propensity to cause metabolic changes have been studied. Some researchers propose that this

variability in the receptor profiles is responsible for the differential liability to induce metabolic changes(66,70). Antagonist activity on muscarinic receptors has been hypothesised to induce weight gain. Effect on the dopamine reward system as an antagonist can facilitate appetite and hence increase weight (71). The direct effect of antipsychotic medication on pancreatic function has been supposed to be the cause for irreversibility of weight gain even after discontinuation of the medications (66,67,70).

Some recent studies have shown that the child and adolescent populations are more prone to metabolic side effects of antipsychotic medication in comparison to adult populations(72,73).

Study	Country	N	Design	Mean age
De Hert et al (71)	Belgium	31	Baseline aripiprazole	36.7
			Endpoint aripiprazole	36.7
Attux et al (64)	Brazil	44	First episode 6 months	26.3
De Hert et al (73)	Belgium	155	After 3 months SGA	33.7
		16	After 3 months amisulpride	33.7
		16	After 3 months aripiprazole	33.7
		20	After 3 months clozapine	33.7
		45	After 3 months olanzapine	33.7
		21	After 3 months quetiapine	33.7
		37	After 3 months risperidone	33.7
L'Italien et al (79)	USA	91	Placebo trials, placebo	41.4
		151	Placebo trials, aripiprazole	40.7
		212	Active comparator trials, olanzapine	37.7
		198	Active comparator trials, aripiprazole	37.6
Saddichha et al (89)	India	30	First episode 6 weeks	26.9
Srisurapanont et al (95)	Thailand	35	Naturalistic 1 year follow-up	34.7
De Hert et al (74)	Belgium	122	First episode, 3 year FGA	26.8
		108	First episode, 3 year SGA	25.1
		8	First episode, 3 year amisulpride	25.1
		10	First episode, 3 year aripiprazole	25.1
		12	First episode, 3 year clozapine	25.1
		34	First episode, 3 year olanzapine	25.1
		24	First episode, 3 year quetiapine	25.1
		20	First episode, 3 year risperidone	25.1
Meyer et al (84)	USA	164	Baseline olanzapine	40.9
			After 3 months olanzapine	40.9
		147	Baseline risperidone	40.9
			After 3 months risperidone	40.9
		143	Baseline quetiapine	40.9
			After 3 months quetiapine	40.9
		77	Baseline ziprasidone	40.9
			After 3 months ziprasidone	40.9
		129	Baseline perphenazine	40.9
			After 3 months perphenazine	40.9
Schorr et al (93)	Netherlands	260	12 months incidence	41.0
			12 months reversibility	37.0

FGA – first-generation antipsychotic; SGA – second generation antipsychotic; ATP - Adult Treatment Panel; IDF - International

Indian scenario

The prevalence of the metabolic syndrome shows variations not only between countries but also between ethnicities within a given region.(74,75) Since metabolic syndrome is a construct to identify people at increased risk of developing diabetes, the identification of this syndrome is of special significance in a country like India which has one of the largest number of people with diabetes mellitus in the world(76) .

There has been a trend of increase in both metabolic syndrome and obesity in South Asian countries including India accounting for the increased rates of morbidity and mortality due to cardiovascular disease and diabetes mellitus(77)(78). Some estimates state that about one third of south Asians residing in urban settings have the metabolic syndrome(79). The term “South Asians” is used to identify people from India, Bangladesh, Bhutan, Maldives, Nepal, Pakistan, and Sri Lanka. The higher prevalence of diabetes mellitus among the South Asian population despite lower rates of obesity (when defined by the traditional body mass index criteria) is called the South Asian Paradox(77,78). Some researchers attribute to the peculiar phenotype of people from this part of the globe, called the South Asian Phenotype. This is characterised anthropometrically by increased waist circumference, increased waist hip ratio and excessive body fat mass. The classic Indian lipid triad is low levels of HDL cholesterol, elevated levels of triglycerides and elevated LDL cholesterol(80–82). In other studies the blood parameters are characterised by increased plasma insulin levels, increased triglycerides, low levels of HDL cholesterol, insulin resistance and atherogenic dyslipidemia(77,78). Taking off from this concept one subset analysis which was part of the landmark Chennai Urban Rural Epidemiology Study (CURES) was comparison of the prevalence of coronary artery disease between metabolic obesity and phenotype obesity(83). This study showed initially that the prevalence of

coronary artery disease was higher in metabolically obese in comparison to the metabolically healthy obese phenotype, this difference did not hold true when age standardization was done(83). Independent studies on the prevalence of metabolic syndrome have been conducted in different parts of India (39)(84)(85)(86,87). There is unfortunately a dearth of periodic nationwide data and surveillance protocols in India to monitor metabolic syndrome(88,89). The prevalence rates vary from 18.3% (39) to as high as 33.5%(87). There are however differences in the diagnostic guidelines employed by these studies. The CURES study which is one of the largest epidemiological studies on diabetes conducted in India made comparison of the prevalence rates based on whether the WHO, IDF or ATP III guidelines were used. The study concluded that each of these guidelines identify different types of individuals and that the WHO criteria identified greater number of subjects with cardiovascular disease, though mainly in males(39). Most of the studies have used the ATP III criteria. The metabolic syndrome is found to have a higher prevalence in women (86,87). Other risk factors that have been identified include older age, inadequate fruit intake and middle to high socio-economic status (87). One study concluded that the elements of the metabolic syndrome which are abnormal in women include increased waist circumference, elevated BMI, low HDL cholesterol and hyperglycaemia while in men these were predominantly elevated triglycerides and hypertension(86).

Early death in mental illnesses like Schizophrenia has been attributed to cardiovascular diseases(46,90). A number of studies have been conducted in India on the prevalence of metabolic syndrome in antipsychotic naive patients with schizophrenia(53,54,56,57,91–95). These have had limitations in terms of small sample sizes and heterogeneity in diagnostic criteria used to define the metabolic

syndrome. One recent study pooled the information from the existing studies(96). This included pooled data from the northern(53,54,92), central(57,93,94) and southern(56,95) regions of India. Using the joint interim statement guidelines(37), this study has shown that one fifth of patients with schizophrenia from India who are antipsychotic naive have metabolic syndrome(96).

Metabolic profile in Antipsychotic naive Indian patients (pooled data)(96)

Variable	Total (*n*=137) Frequency (%)	Male (*n*=69) Frequency (%)	Female (*n*=68) Frequency (%)	χ^2 value
1**P*<0.05; ***P*<0.01, ****P*<0.001. 1. †Fisher's exact test. 2. BMI, body mass index; HDL, high-density lipoprotein.				
Systolic blood pressure ≥130 mmHg	33 (24.1)	18 (26.0)	15 (22.1)	0.30
Diastolic blood pressure ≥85 mmHg	27 (19.7)	19 (27.5)	8 (11.8)	5.38*
Abnormal blood pressure (≥130//≥85) or diagnosed as hypertensive	37 (27.0)	21 (30.4)	16 (23.5)	0.82
Triglyceride levels ≥150 mg or on lipid-lowering agents	24 (17.5)	18 (26.1)	6 (8.8)	7.06**
Lower HDL (<40 mg M, <50 mg F) or on lipid-lowering agents	81 (59.1)	31 (44.9)	50 (73.5)	11.59**
Fasting blood glucose levels ≥100 mg % or diagnosed as diabetes mellitus	28 (20.4)	15 (21.7)	13 (19.1)	0.14

Variable	Total (*n*=137) Frequency (%)	Male (*n*=69) Frequency (%)	Female (*n*=68) Frequency (%)	χ^2 value
Abnormal waist circumference (≥90cm for men and ≥80 cm for women)	38 (27.7)	15 (21.7)	23 (33.8)	2.49
Obesity (BMI≥25 Asian cut-off)	25 (18.2)	16 (23.2)	9 (13.2)	2.27
Underweight (BMI<18.5)	51 (37.22)	22 (31.8)	29 (33.8)	1.69
Metabolic syndrome (common criteria for clinical diagnosis)	26 (19)	13 (18.8)	13 (19.1)	0.002
No. of metabolic syndrome criteria†				
0	23 (16.8)	14 (20.3)	9 (13.2)	–
1	56 (40.9)	27 (39.1)	29 (42.6)	–
2	32 (23.3)	15 (21.7)	17 (25)	–
3	21 (15.3)	11 (15.9)	10 (14.7)	–
4	2 (1.5)	1 (1.4)	1 (1.5)	–
5	3 (2.2)	1 (1.4)	2 (2.9)	–

Studies from India on the prevalence of metabolic syndrome in patients on antipsychotic medications are limited. Most studies have reported a prevalence rate ranging from 3.3 to 68% with an average of 35% irrespective of the diagnostic guideline used to define the metabolic syndrome(91)(97). One recent study clearly demonstrated the increase in the prevalence when maximum dosages of antipsychotic medications were used(98). One other study reaffirms the current understanding of increased risk of metabolic syndrome with the use of Olanzapine in particular when

compared to other second generation antipsychotic medications(99). Majority of the studies have used cross-sectional design(100,101). Prospective interventional studies in India are few (99,102–104). These studies were of short durations ranging from 6 weeks to 4 months. Most of them were done on patients with schizophrenia (53,93,99,100,103).

Two studies have been done on metabolic syndrome in people with bipolar illness, which have identified central obesity as key risk factor and the prevalence to be higher than in patients with schizophrenia(101,102).

Attrition rates in Psychiatric clinical trials

Longitudinal studies have reported large attrition rates in clinical trials among psychiatric populations (105–107). Numerous variables have been described to be risk factors towards attrition from psychiatric clinical trials. These are broadly divided into socio-demographic variables, lifestyle variables and psycho-pathology related variables. Some studies have enumerated low educational level, unemployed status, being single or divorced as the socio-demographic variables that lead to high rates of attrition (107–109). Unhealthy lifestyle variables described in literature to be associated with high attrition rates include lack of physical activity, use of tobacco and alcohol (109–111). Studies have also highlighted high rates of attrition among psychiatric patients with previous history of hospitalization and in those using outpatient facilities (106,112). Types of attrition have been categorised into refusal, non-contact and death. Non-contact can be of two types: those who were unable to participate and those who could not be contacted. An understanding of the mechanisms underlying these types of attrition gives insight into the determinants involved (113). Research has shown that being of younger age, lesser degree of

formal education, no prior history of participation in research and having depressive illness as determinants associated with drop out in European population (114). No major differences have been found between the effects of these determinants on the type of attrition. People with depressive and anxiety illnesses have been reported to be at 2.4 times higher risk of dropping out (114).

Screening and Monitoring guidelines in Psychiatric population

At the onset of initiating therapy with antipsychotic medications, prevention of the development of metabolic syndrome should be given high priority. Hence the initiation of exercise, diet and lifestyle modification strategies should start prophylactically, while the medication is being started.

There is a lack of consensus regarding the responsibility to mentally ill patients regarding general health care. This is reflected in the failure to provide adequate and appropriate health care to this subset of the population. In routine practise the psychiatrist's main focus is on the effectiveness of the antipsychotic therapy. As a result the general medical needs of the patient are inadvertently neglected.

In spite of the numerous national and international guidelines for monitoring of metabolic syndrome, these are rarely enforced in routine clinical practise (115–117).

Assessment of the metabolic risk profile before the initiation of antipsychotic therapy is important. The sensitivity in identifying patients with metabolic syndrome using waist circumference and fasting glucose measures is as high as 100%. This emphasises that cardio-metabolic risk profile assessment is a must before the commencement of treatment (118).

In order to prevent the metabolic complications the non-pharmaceutical interventions like lifestyle interventions, diet modifications and physical exercise regimen need o be

started early in therapy (46). Timely institution of these interventions reduces the risk significantly. Cessation of smoking reduces the prevalence of cardiovascular disease by 50-70%. Reducing the cholesterol levels by 10% bring about a 30% reduction in the cardiovascular disease risk. Similarly a 15% reduction in the cardiovascular risk can be obtained by reducing the blood pressure by 6%. The cardiovascular disease risk can be reduced by 30 to 50% by combined strategies of a 20 minutes brisk walk a day coupled with maintaining the body mass index below 25 (46).

The role of regular physical activity in reducing both cardiovascular disease and metabolic risk is undisputed (119). In the prevention of dyslipidemia, diabetes, hypertension and obesity, regular physical activity is of great importance (120, 121). Hence lifestyle modification interventions in schizophrenia should incorporate regular physical exercise. Though the guidelines do not give recommendations to the type and duration of the physical activity for patients with schizophrenia, 30 minutes brisk walk on at least 5 days a week should suffice to reduce the metabolic risk significantly. Ample attention should be paid to the patient's personal preference and attitude towards physical activity while selecting the activity (119,122).

Interventions to stop cigarette smoking are also of great importance in the prevention of metabolic syndrome (123). Awareness should be present in the clinicians mind regarding patients who are elderly, with family history of metabolic risk factors and or are of ethnic group with high susceptibility for metabolic syndrome, while prescribing antipsychotic medication (123).

Once a patient develops metabolic syndrome, switching to a different antipsychotic medication that has reduced potential to cause metabolic effects should be the strategy employed. Along with this, measures to reduce cholesterol and triglycerides along with controlling the blood sugar and blood pressure should be put in place. During this process, consultation with a specialist should be sought as and when required. Though there is recent evidence of the efficacy and safety of statins in patients with schizophrenia on antipsychotic medications, their role in reversing the metabolic syndrome is not very significant (124,125).

OBJECTIVES AND AIMS

Primary Objectives:

- To estimate the prevalence of metabolic syndrome in antipsychotic naïve psychiatric patients at the recruitment phase as defined by the National Cholesterol Education Program's Adult Treatment Panel III and to compare with the International Diabetes Federation criteria.

- To estimate the incidence of metabolic syndrome in antipsychotic naïve patients, 3 months after the initiation of therapy with antipsychotic medication using the guidelines as defined by the National Cholesterol Education Program's Adult Treatment Panel III.

Secondary Objectives:

- To identify the risk factors associated with metabolic syndrome in antipsychotic naïve patients.

- To identify the risk factors that predicts the emergence of metabolic syndrome after initiation of antipsychotic therapy.

METHODOLOGY

Setting:

The study was conducted in the Department of Psychiatry, Christian Medical College Vellore. This is a tertiary care teaching hospital in the southern part of India. This facility has an in-patient capacity of 122 beds including adult, child and adolescent services. There is an acute care room comprising of 12 beds. Most of the patients are self referred and come from all over India.

The facilities also include well equipped outpatient department, occupational therapy, pharmacy services and emergency services. The outpatient department functions six days in a week. Here both new and review patients are seen and followed up. Emergency services are available 24 hours a day, seven days a week.

The institution has the facilities of a tertiary care referral centre. In addition to this it serves as the nearest psychiatric centre for a radius of 150 miles. The department has four units, two serving the needs of adult clients, one for children & adolescents and one for rehabilitation services. Every year this centre caters to the needs of 11000 new patients and 90000 review patients. Per annum on an average 1000 patients are provided inpatient treatment services.

Participants:

Subjects for the study were recruited from both in-patient and out-patient facilities in the department of Psychiatry. Attempts were made to follow up these patients over 3 months period. A follow up period of 3 months was chosen as there is evidence that the metabolic changes due to antipsychotic treatment are seen as early as around 3 months of treatment(126,127).

Inclusion criteria:

1) Age between 18 and 65 years

2) Any patient who is antipsychotic naive and is started on antipsychotic medication

3) As the patients need to be followed up after 3 months, for logistic reasons, participants will only be recruited from the state of Tamil Nadu.

Exclusion criteria

1) Age lesser than 18 and above 65 years

2) Pre-existing metabolic syndrome

3) Patients on combinations of antipsychotic medications with mood stabilizers or tricyclic antidepressants or Mirtazapine, which may contribute to the incidence of metabolic syndrome.

4) Those who could not participate either due to the severity of illness or refusal to take part

Variables:

Variables assessed included

1. Socio-demographic: age, sex, marital and employment status
2. Individual metabolic parameters
3. Family history of medical morbidity (diabetes mellitus, hypertension, dyslipidemia, obesity)
4. Antipsychotic medication: type and dose

Institutional Review Board:

The approval of the Institutional Review Board of the Christian Medical College-Vellore was obtained before the commencement of the study.

Data Sources/measurement:

Patients attending the psychiatric OPD, inpatient and emergency services were screened. Those meeting the inclusion criteria were enrolled into the study after obtaining a written informed consent.

Demographic data including age, sex, occupational and marital status, substance use, family history of medical illness was collected from the patient and relative.

Subsequently blood pressure, height, body weight and waist circumference were measured and documented.

Blood pressure measurement (128): Mercury sphygmomanometer was used for the measurement of the blood pressure. Patients were require to be seated quietly for at least 5 minutes in a chair with back supported, legs uncrossed and upper arm bared. Patient's arm was supported at heart level. Measurement was taken with a cuff size that was appropriate to the size of the upper right arm. The right arm was preferred for consistency and comparison with the standard tables. The bell of the stethoscope was lightly placed over the brachial artery pulse, proximal and medial to the cubital fossa, and below the bottom edge of the cuff (i.e., about 2 cm above the cubital fossa). The cuff was inflated to 30 mm Hg above palpated SBP and deflated at a rate of 2 to 3 mm Hg/second. Both Systolic Blood Pressure (SBP) and Diastolic Blood Pressure were recorded. The first appearance of sound (phase 1) was used to define SBP. The disappearance of sound (phase 5) was used to define DBP in adults. Two or more

readings separated by 2 minutes were averaged. If the first two readings differ by more than 5 mm Hg, additional readings were obtained and averaged. Subject as well as the examiner did not talk during the procedure.

Waist circumference (129): The same standardized tape was used for each measurement. Subject was required to stand with feet positioned close together, arms at the sides, erect with weight distributed evenly. The subject was advised to relax and take a few natural breaths before actual measurement is made. Measurement was made at the end of each expiration (when lungs are at their functional residual capacity). Tape measurement (in centimetres) was taken with the tape aligned at points immediately above the iliac crests on either side. The tape was snugly pulled around the waist but not too tight that it was constricting. In compliance with the IDF criteria we also measured the waist circumference in a horizontal plane across the umbilicus, midway between the inferior margin of the ribs and the superior border of the iliac crest.

Weight and height were also measured using the same calibrated analogue weighing scale and wall-meter respectively. During the measurement of weight it was ensured that the participants were barefooted, bareheaded, without any items of weight on their body, weight evenly distributed across both feet, standing erect. While measuring the height, the individual was asked to stand erect, barefooted with both feet together adjacent to the wall meter, and looking ahead. It was ensured that the heels, buttocks, shoulders, and head were back against the wall and that all of those body parts were touching the wall. Participants were asked to tuck in their chin and look straight ahead. A book was placed on the subject's head (the same book was

used for all subjects), pressed on to the wall meter, and the place on the wall meter where the bottom of the book was resting was marked.

Patients were asked to do fasting blood glucose and fasting triglycerides and HDL cholesterol within a week's time. The blood was taken using sterile methods by a trained technician.

Attempts were made to review the patients after a period of three months to repeat the collection of all the information collected during the enrolment phase.

Bias:

Consecutive patients attending the psychiatric services were recruited to reduce selection bias.

Sample size:

Sample size was calculated using a previous study which estimated the incidence of treatment emergent metabolic syndrome in 3 months as 11% (130).

The following assumptions were made for the calculation of the sample size:

Incidence = 11%

Margin of error (precision) = ±6

Confidence level = 95%

Power = 80%

Drop out during follow up = 50%

Total required sample size = 216

Quantitative variables:

Mean and standard deviation would be employed to describe continuous variables, while frequency distributions would be obtained for categorical data. The chi square test and the Student's t-test would be used to assess the significance of associations for categorical and continuous variables respectively.

Statistical methods:

The paired t test would be employed to assess the change over time in continuous variables.

Bi-variate analyses would be done to find factors associated with metabolic syndrome using either chi-square tests or independent two sample t=tests as appropriate. Variables with a $p<0.10$ would subsequently be used in the multivariable logistic regression analysis. Odds ratios with 95% CI would be obtained to quantify the association between medication and other factors.

Data Collection:

Patients were referred for the study by colleagues based on the inclusion and exclusion criteria. These patients were screened by the study author using the inclusion and exclusion criteria. At the time of screening an informed written consent was obtained from the patient whenever possible. Written informed consent was obtained from the primary care giver when the patient lacked capacity to do so. Contact telephone numbers to prevent attrition from the study was collected after

taking informed verbal consent. Thereafter the patient was given the slips for the blood investigations to be done in a fasting state within one week. Patients were recruited only if they did the blood investigations within the stipulated time period. Anthropometric details and other relevant data were collected only after the completion of the blood investigations.

Data analysis:

Data analysis was done using SPSS Statistic software version 20.

RESULTS

Flowchart of the study

A total of 314 patients were screened for the study. They were referred by colleagues based on the inclusion and exclusion criteria. Out of these 314 subjects, 31 declined consent. 135 participants could not be recruited into the study. 39 patients gave informed consent at the time of the index visit, but did not follow up in the outpatient services thereafter. As mentioned in the methodology, patients were recruited contingent on the blood investigations being done within one week of the start of the antipsychotic medications. 44 out of the 135 patients did the blood investigations outside the planned cut off of a week. These blood investigations were late by one day to two weeks. Another 16 patients reviewed with incomplete blood investigations. Some had not given fasting sugars; others had not given their lipid profile. 36 patients did not do any of the blood investigations.

148 patients out of the total 314 patients screened entered into the study based on the satisfaction of the inclusion criteria, and blood investigation requirements. Baseline blood investigations coupled with the anthropometric measurements revealed that 28 out of the 148 antipsychotic naive patients had metabolic syndrome according to NCEP- ATP III criteria. These patients were hence removed from the cohort.

Of the remaining 120 participants, 89 were lost to follow up in terms of not using the outpatient services. Attrition in terms of mortality is not known. Attempts were made to reduce the attrition by calling the patient or caregivers by phone. The reasons for attrition included improvement in symptoms, complete resolution of symptoms and promises of following up which were not met. The required blood investigations were not done at the time of review by 8 subjects even though they continued to use the outpatient services and hence could not be used in the analysis. 14 patients, who were compliant with the medications, were followed up according to the study guidelines

and could be assessed for the emergence of metabolic syndrome. 9 of the 148 subjects had been recruited in August 2014 and were not included at the time of analysis (September 2014) as they would complete 3 months of antipsychotic therapy only by October 2014. Data collection was incomplete due to advancement of the date of submission of the thesis by 2 months that was announced in July and confirmed in August 2014.

A total of 148 patients were recruited into the study after obtaining written informed consent. 14 subjects were followed up after 3 months for incidence of metabolic syndrome. 28 subjects had metabolic syndrome before the start of antipsychotic medications. 97 subjects were lost to follow up. 9 had not completed the study period.

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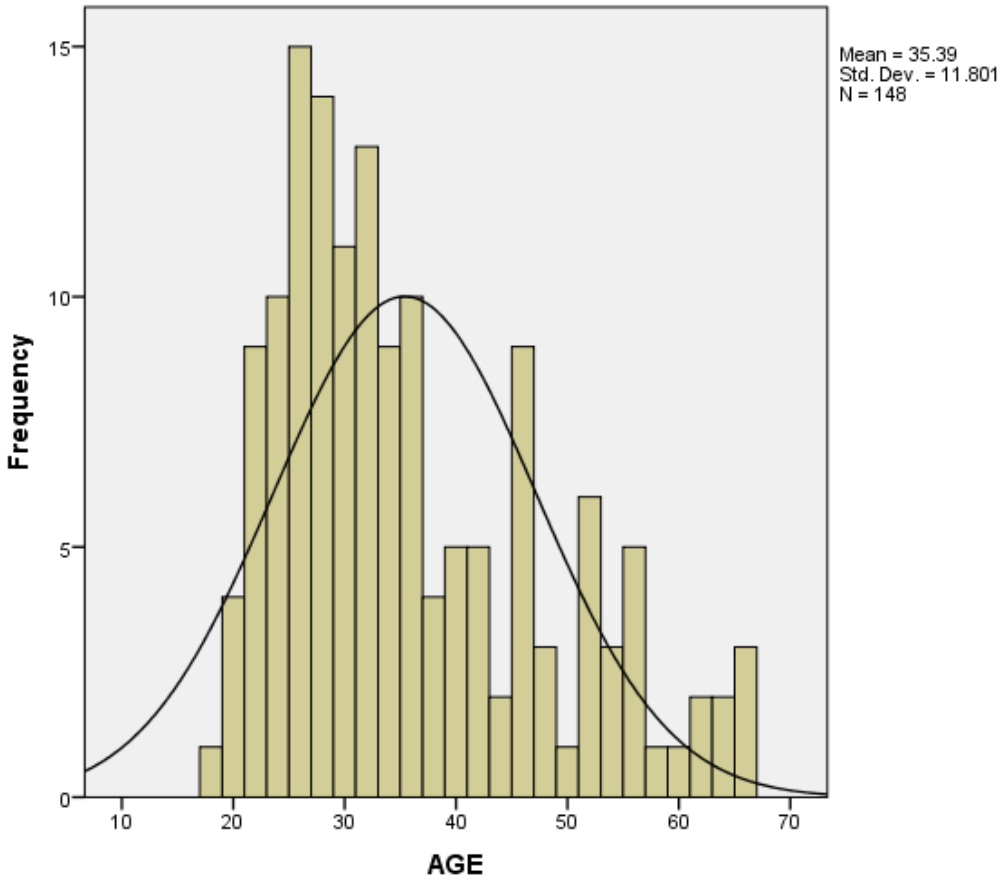
Age distribution of the patients recruited at baseline



As depicted in the histogram, the mean age of the selected sample was 35. The standard deviation was 12 years. The youngest recruit was 18 years old. The oldest participant was 65 years old.

Out of the 148 participants who were recruited 72 were male and 76 were female. The mean age of the subjects was 36 years. Of the participants 44 were single, 98 were married, and 6 were widowed or separated. 30 subjects were illiterate while the remaining 118 were literate.

SOCIO-DEMOGRAPHIC, DIET AND SUBSTANCE USE DISTRIBUTION AMONG THE PATIENTS AT BASELINE

VARIABLE		NUMBER OF PATIENTS	PERCENTAGE	TOTAL NUMBER OF PATIENTS AT BASELINE
GENDER	MALE	72	49	**148**
	FEMALE	76	51	
MARITAL STATUS	SINGLE	44	30	**148**
	MARRIED	98	66	
	DIVORCED / WIDOWED	6	4	
EDUCATION	ILLITERATE	30	20	**148**
	LITERATE	118	80	
DIET	VEGETARIAN	20	13	**148**
	NON-VEGETARIAN	128	87	
TOBACCO USE*	ABSENT	121	82	**148**
	PRESENT	27	18	
ALCOHOL USE*	ABSENT	128	87	**148**
	PRESENT	20	13	

* Use does not amount to a dependence pattern

Distribution according to the diet and prevalence of metabolic syndrome (NCEP-ATP III criteria) at baseline

NCEP- ATP III CRITERIA		DIET		Total
		VEGETARIAN	NON-VEGETARIAN	
NCEP ATP Criteria satisfied	Nil criteria	4	35	39
	1 criteria	7	43	50
	2 criteria	6	25	31
	3 criteria	3	25	28
Total		20	128	148

The above table illustrates the distribution of the participants at the time of recruitment into the study based on the type of diet and satisfaction of the NCEP-ATPIII criteria. Statistical analysis of the association between type of diet and the prevalence of metabolic syndrome was done. Analysis was also done comparing type of diet with the prevalence sub-threshold metabolic syndrome (either satisfying only 2 or only 1 criterion out of the 5 NCEP-ATPIII criteria). The analysis was done using Chi square test which gave Pearson Chi-Square value of 1.457 with Fisher's Exact Test p value of 0.704. This was not statistically significant.

Distribution according to use of tobacco and prevalence of metabolic syndrome (NCEP-ATP III criteria) at baseline

NCEP- ATP III CRITERIA		TOBACCO USE		Total
		ABSENT	PRESENT	
NCEP ATP Criteria satisfied	Nil criteria	36	3	39
	1 criteria	39	11	50
	2 criteria	25	6	31
	3 criteria	21	7	28
Total		121	27	148

The above table illustrates the distribution of the participants at the time of recruitment into the study based on the use of tobacco and satisfaction of the NCEP-ATPIII criteria. Statistical analysis of the association between use of tobacco and the prevalence of metabolic syndrome was done. Analysis was also done comparing use of tobacco with the prevalence sub-threshold metabolic syndrome (either satisfying only 2 or only 1 criterion out of the 5 NCEP-ATPIII criteria). The analysis was done using Chi square test which gave Pearson Chi-Square value of 4.267 with Fisher's Exact Test p value of 0.185. This was not statistically significant.

Distribution according to use of alcohol and prevalence of metabolic syndrome (NCEP-ATP III criteria) at baseline

NCEP- ATP III CRITERIA		ALCOHOL USE		Total
		ABSENT	PRESENT	
NCEP ATP Criteria satisfied	Nil criteria	37	2	39
	1 criteria	45	5	50
	2 criteria	24	7	31
	3 criteria	22	6	28
Total		128	20	148

The above table illustrates the distribution of the participants at the time of recruitment into the study based on the use of alcohol and satisfaction of the NCEP-ATPIII criteria. Statistical analysis of the association between use of alcohol and the prevalence of metabolic syndrome was done. Analysis was also done comparing use of alcohol with the prevalence sub-threshold metabolic syndrome (either satisfying only 2 or only 1 criterion out of the 5 NCEP-ATPIII criteria). The analysis was done using Chi square test which gave Pearson Chi-Square value of 6.556 with Fisher's Exact Test p value of 0.081. This was not statistically significant.

DISTRIBUTION ACCORDING TO THE PRESENCE OF FAMILY HISTORY OF RISK FACTORS AMONG THE PATIENTS AT BASELINE

FAMILY HISTORY OF		NUMBER OF PATIENTS	PERCENTAGE	TOTAL NUMBER OF PATIENTS AT BASELINE
HYPERTENSION	ABSENT	138	93	**148**
	PRESENT	10	7	
DIABETES MELLITUS	ABSENT	136	92	**148**
	PRESENT	12	8	
DYSLIPIDEMIA	ABSENT	139	94	**148**
	PRESENT	9	6	
OTHER*	ABSENT	145	98	**148**
	PRESENT	3	2	

***-** These illnesses included two with family history of seizure disorder and one with family history of stroke.

DISTRIBUTION OF THE VARIOUS INDIVIDUAL COMPONENTS OF THE METABOLIC SYNDROME AMONG THE PATIENTS AT BASELINE

Criterion		Number of patients	Percentage	Total number of patients at baseline
WAIST CIRCUMFERENCE	NORMAL	124	84	**148**
	INCREASED (males ≥ 90 cm, females ≥ 80 cm)	24	16	
BLOOD PRESSURE	NORMAL	118	80	**148**
	INCREASED (≥130/≥85 mm Hg)	30	20	
FASTING BLOOD SUGAR	NORMAL	116	78.	**148**
	ELEVATED (≥100 mg/dl)	32	22.	
TRIGLYCERIDES	NORMAL	112	76	**148**
	ELEVATED (≥150 mg/dl)	36	24	
HDL CHOLESTEROL	NORMAL	65	44	**148**
	LOWERED (< 40 mg/dL males; < 50 mg/dL females)	83	56	

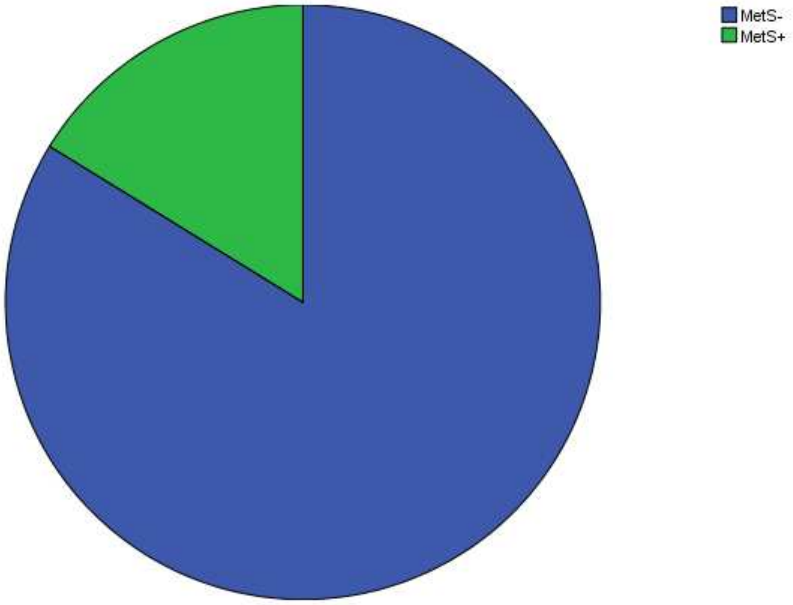
Distribution of the means of the variables at the baseline

VARIABLE	MEAN	STANDARD DEVIATION	MINIMUM VALUE	MAXIMUM VALUE
AGE (years)	36	12	18	65
WAIST CIRCUMFERENCE (cm)	75.85	11.9	29	106
SYSTOLIC BLOOD PRESSURE (mmHg)	117.9	10.2	90	150
DIASTOLIC BLOOD PRESSURE (mm Hg)	78.07	6.26	60	100
FASTING BLOOD SUGAR (mg/dL)	94.7	25.77	52	272
HDL CHOLESTEROL (mg/dL)	44.95	13.52	10	121
TRIGLYCERIDES (mg/dL)	127.68	109	34	1018

Prevalence of metabolic syndrome in the patients at baseline (NCEP-ATP III criteria)

METABOLIC SYNDROME	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	120	81
PRESENT	28	19
TOTAL	148	100

Analysis at the time of recruitment showed that based on the NCEP ATP III diagnostic criteria 19 % of the sample satisfied 3 out of the 5 criteria. This means that 28 patients out of the 148 participants recruited had metabolic syndrome even before the start of antipsychotic medications.



MetS- Metabolic Syndrome absent
MetS+ Metabolic Syndrome present

Prevalence of Metabolic syndrome (NCEP ATP III criteria) among the patients at baseline148)

Gender specific distribution in the patients at baseline

Female

METABOLIC SYNDROME IN FEMALES	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	62	81
PRESENT	14	19
TOTAL	76	100

Among the 76 female members recruited at the time of the study, 14 participants had metabolic syndrome prior to the initiation of antipsychotic medication. This is based on the NCEP ATP III criteria. This amounts to 19% prevalence rate among women.

Male

METABOLIC SYNDROME IN MALES	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	58	80
PRESENT	14	20
TOTAL	72	100

Among the 72 male members recruited at the time of the study, 14 participants had metabolic syndrome prior to the initiation of antipsychotic medication. This is based on the NCEP ATP III criteria. This amounts to a prevalence rate of 20% among males.

Gender specific distribution according to the prevalence of metabolic syndrome in the patients at baseline

Gender	Number of participants with metabolic syndrome	Percentage
Male	14	50
Female	14	50
Total	28	100

Comparison of the gender among the antipsychotic naive patients from the baseline population show equal distribution of males and females.

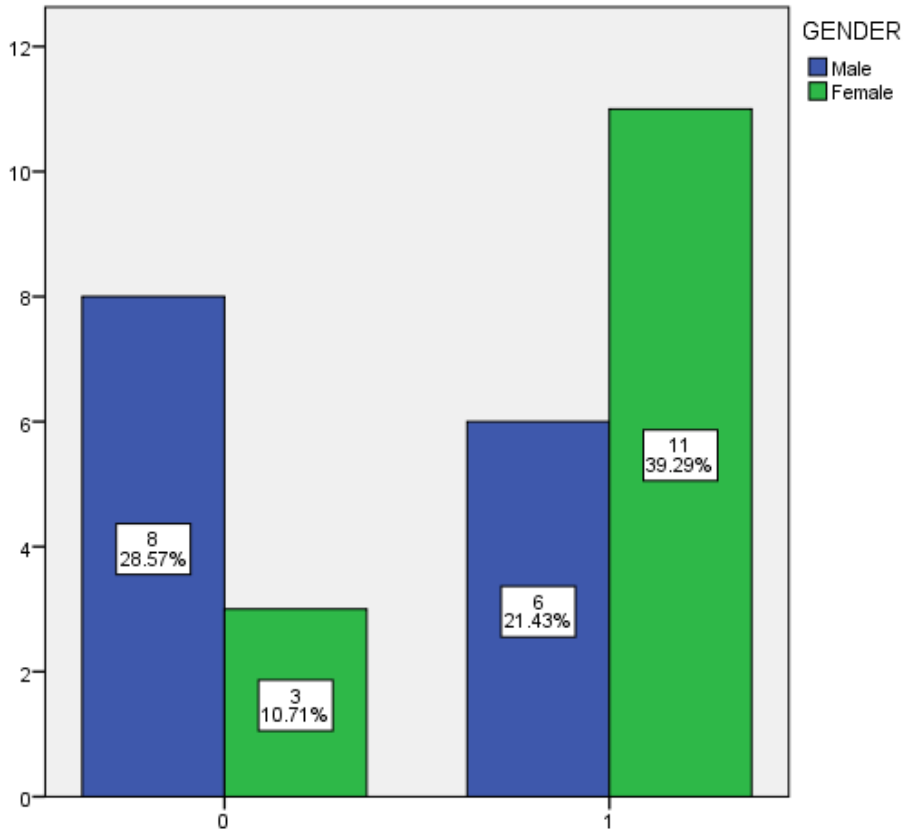
DISTRIBUTION OF THE VARIOUS INDIVIDUAL COMPONENTS OF THE METABOLIC SYNDROME AMONG THE PATIENTS WITH METABOLIC SYNDROME AT BASELINE

Criterion		Number of patients	Percentage	Total number of patients with metabolic syndrome at baseline
WAIST CIRCUMFERENCE	NORMAL	11	39.29	**28**
	INCREASED (males ≥ 90 cm, females ≥ 80 cm)	17	60.71	
BLOOD PRESSURE	NORMAL	11	39.29	**28**
	INCREASED (≥130/≥85 mm Hg)	17	60.71	
FASTING BLOOD SUGAR	NORMAL	8	28.57	**28**
	ELEVATED (≥100 mg/dl)	20	71.43	
TRIGLYCERIDES	NORMAL	11	39.29	**28**
	ELEVATED (≥150 mg/dl)	17	60.71	
HDL CHOLESTEROL	NORMAL	6	21.43	**28**
	LOWERED (< 40 mg/dL males; < 50 mg/dL females)	22	78.57	

Waist circumference in the participants with metabolic syndrome at baseline

Out of the 28 patients who qualified for diagnosis of metabolic syndrome 17 participants had increased waist circumference. This amounts to 61% of those with metabolic syndrome

Analysis based on the gender wise distribution shows that 6 males had waist circumference above 90 cm and 11 females had waist circumference above 80 cm. This amounts to 39.29% and 21.43% respectively.



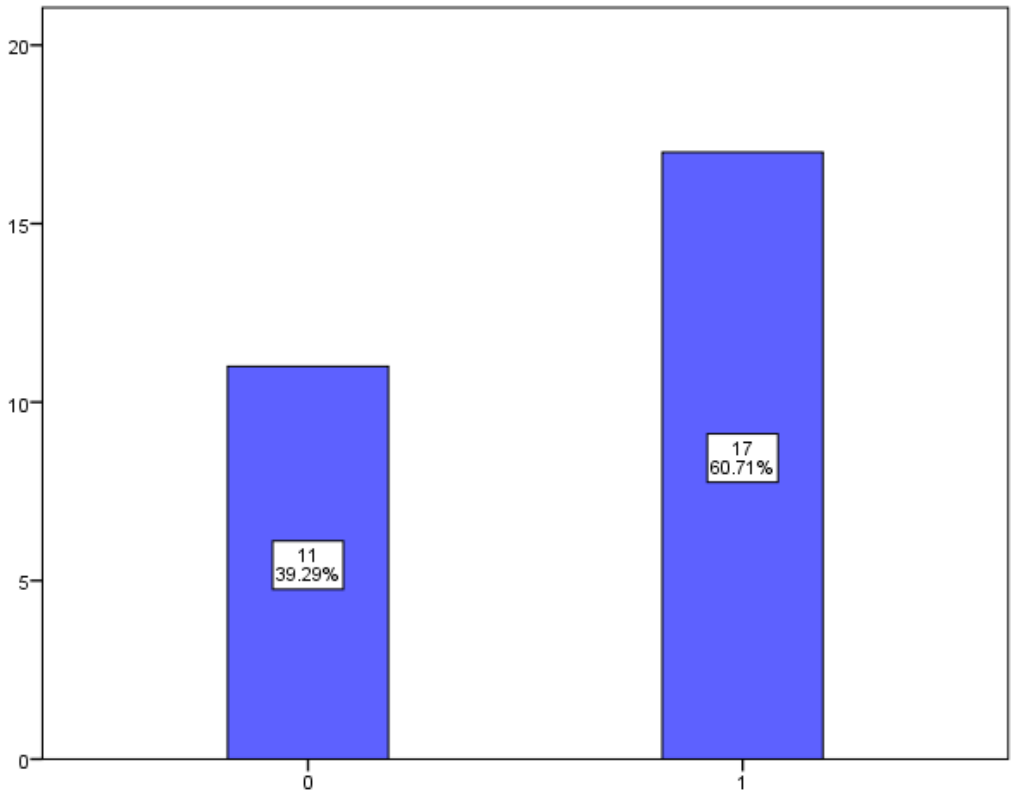
0-<90cm(males); <80cm(females)

1->90cm(males); >80cm(females)

Distribution of the waist circumference among the participants with metabolic syndrome at baseline (n=28)

Blood pressure in the participants with metabolic syndrome at baseline

17 patients from the group of 28 patients who satisfied the diagnosis of metabolic syndrome had blood pressure values above 130/85 mmHg. This signifies that 60.71% of those with metabolic syndrome in this sample had hypertension.



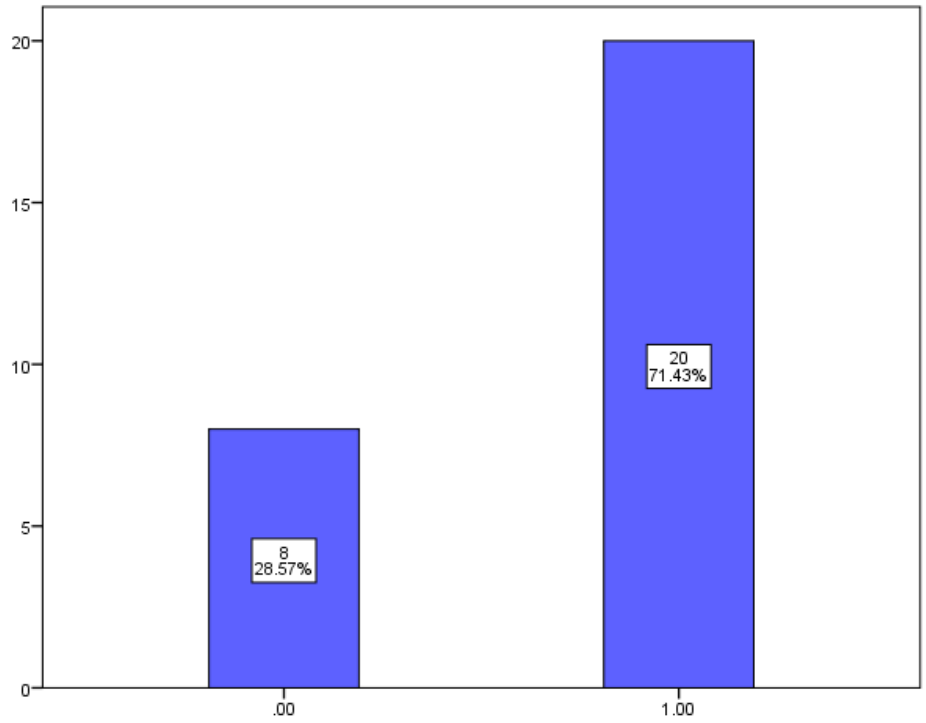
0- < 130mm Hg And <85 mm Hg

1- ≥130mm Hg OR≥85 mm Hg

Distribution of the blood pressure among the participants with metabolic syndrome at baseline (n=28)

Fasting blood sugar levels in the participants with metabolic syndrome at baseline

20 patients with metabolic syndrome in the antipsychotic naive status had fasting blood sugar values above100mg/dl. This means that in this sample of 28 patients with metabolic syndrome, 71% had elevated fasting blood sugars.



.00- < 100 mg/dL

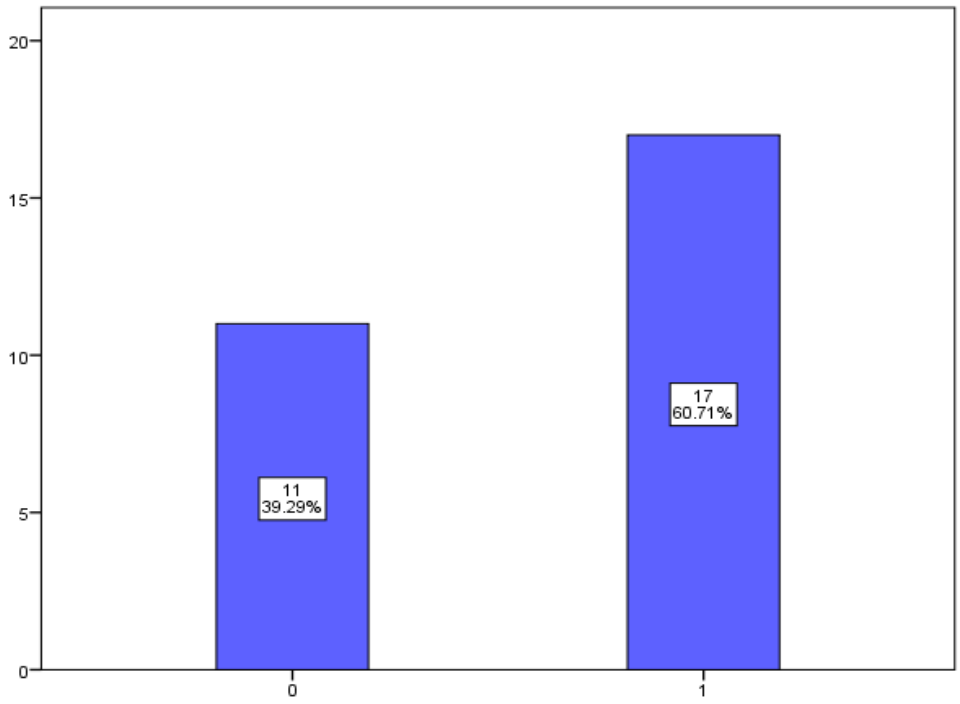
1.00- ≥140 mg/dL

Distribution of the fasting blood sugar levels among the participants with metabolic syndrome at baseline (n=28)

Triglyceride levels in the participants with metabolic syndrome at baseline

Among the 28 patients from the total of 148, who had been diagnosed with metabolic syndrome not induced by antipsychotic medications, 17 patients had elevated triglyceride levels above 150 mg/dl.

So 60.71% of the patients with metabolic syndrome had hypertriglyceridaemia.



0- <150 mg/dL

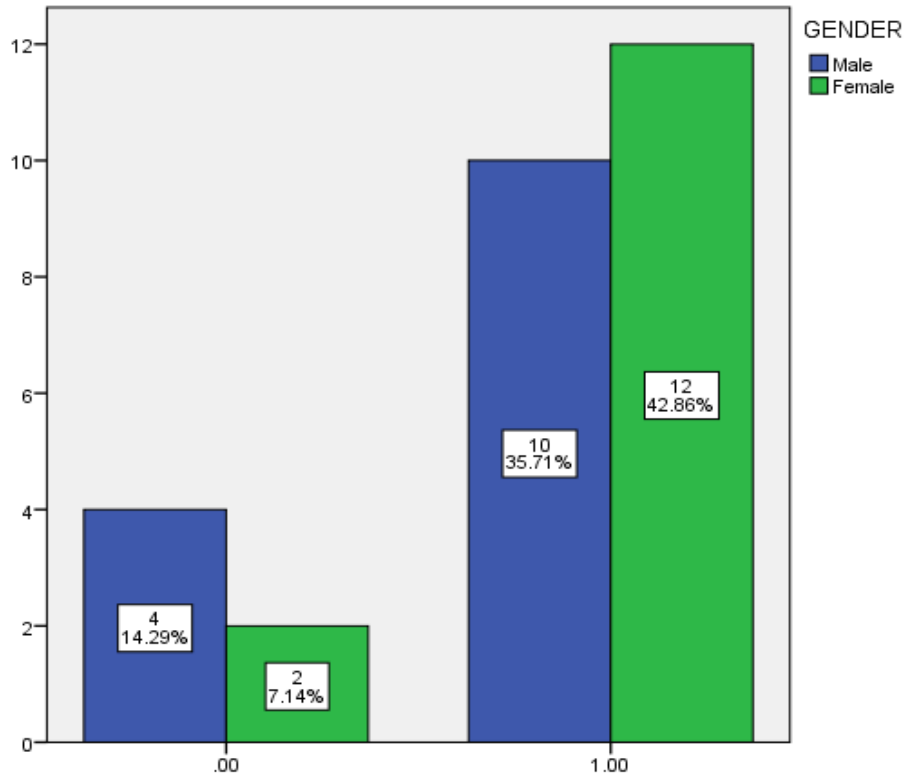
1- ≥150 mg/dL

Distribution of the triglyceride levels among the participants with metabolic syndrome at baseline (n=28)

HDL cholesterol levels in the participants with metabolic syndrome at baseline

From the group of 28 patients identified to have metabolic syndrome at the onset of the study, 22 subjects had low levels of HDL cholesterol. This means that 79% of the patients who qualified for a diagnosis of metabolic syndrome using the NCEP ATP III definition had low levels of HDL cholesterol.

Gender wise distribution shows that 12 out of the 22 patients with metabolic syndrome who had abnormal HDL cholesterol values belonged to the female gender. As depicted by the graph below, females contributed by 42.86% and males by 35.71%.



.00- > 40 mg/dL(males); >50 mg/dL (females)

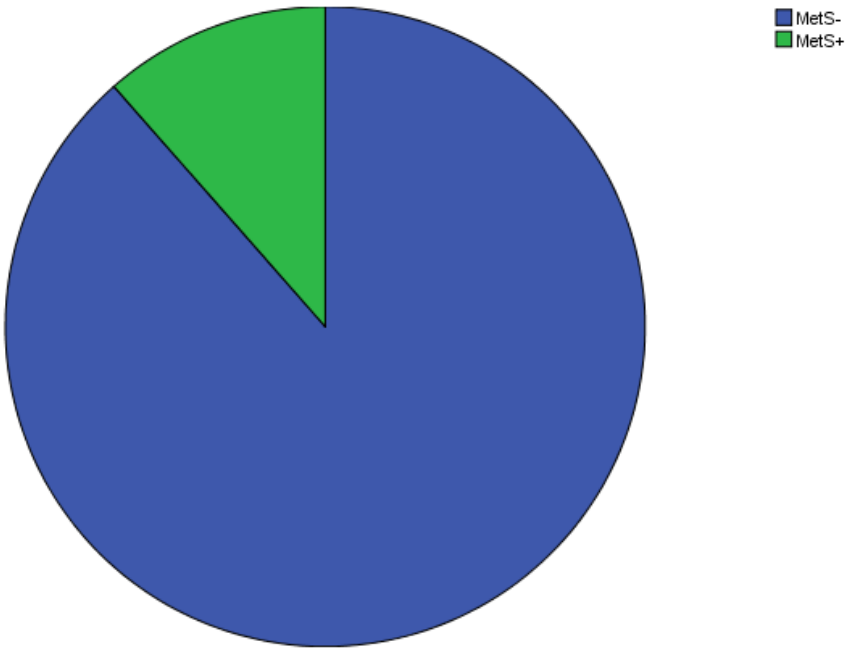
1.00- < 40 mg/dL(males); < 50 mg/dL (females)

Distribution of the triglyceride levels among the participants with metabolic syndrome at baseline (n=28)

Prevalence of metabolic syndrome in the patients at the time of recruitment (IDF criteria)

METABOLIC SYNDROME	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	131	88
PRESENT	17	12
TOTAL	148	100

Analysis of the participants recruited at the baseline of the study showed that based on the IDF criteria, 12% of the sample met the diagnosis of Metabolic syndrome, that is satisfying the waist circumference criteria and one out of 4 criteria. As shown in the table, 17 patients met these criteria.



MetS- Metabolic Syndrome absent
MetS+ Metabolic Syndrome present

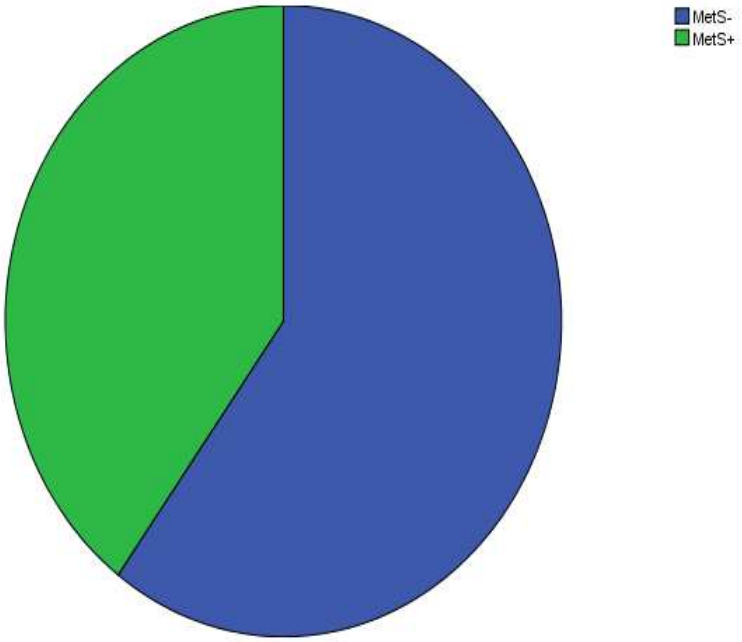
Prevalence of the Metabolic Syndrome among the patients recruited (n=148) based onthe IDF criteria

SUB-THRESHOLD METABOLIC SYNDROME

Prevalence based on satisfying at least two criteria of the metabolic syndrome according to the NCEP ATP III definition

METABOLIC SYNDROME	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	89	60
PRESENT	59	40
TOTAL	148	100

The prevalence of metabolic syndrome in the sample was calculated based on the satisfaction of any two criteria. Based on the presence of any two criteria the overall prevalence of metabolic syndrome increased to 40%. This signifies an increase in the prevalence by 21% as opposed to when the standard definition requiring the satisfaction of 3 criteria (prevalence-19%) is used.



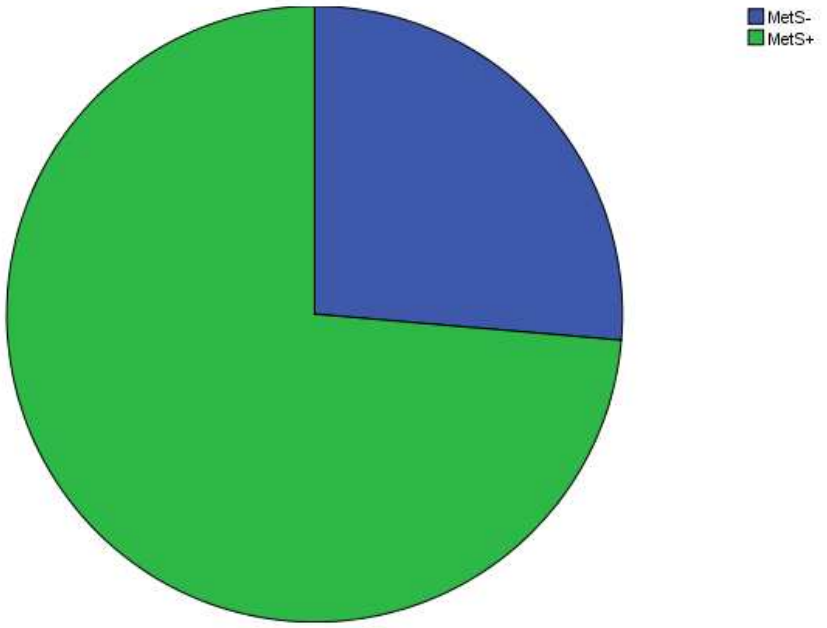
MetS- Metabolic Syndrome absent
MetS+ Metabolic Syndrome present

Prevalence based on satisfying at least two criteria of the metabolic syndrome (NCEP ATP III)

Prevalence based on satisfying at least one criteria of the metabolic syndrome according to the NCEP ATP III definition

METABOLIC SYNDROME	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	39	26
PRESENT	109	74
TOTAL	148	100

When the prevalence of metabolic syndrome using a flexible definition requiring the need to satisfy any one of the five criteria was employed, the prevalence rose to 109 participants out of the total of 148. This signifies a prevalence rate of 74%. This amount to more than 4 times the risk associated when the standard definition of 3 out of 5 criteria is used.



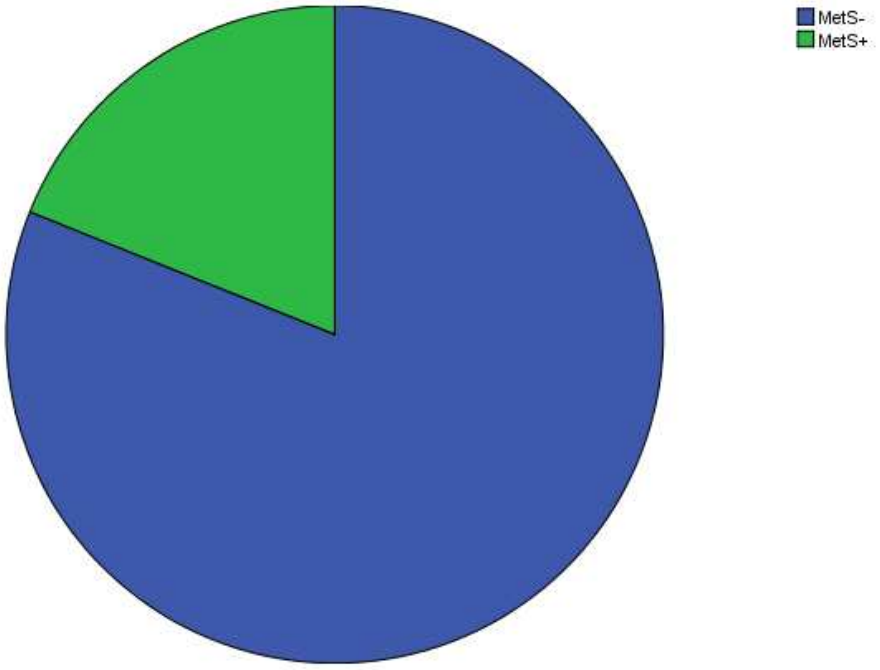
MetS- Metabolic Syndrome absent
MetS+ Metabolic Syndrome present

Prevalence based on satisfying at least one criteria of the metabolic syndrome (NCEP ATP III)

Incidence of metabolic syndrome (NCEP ATP III) among the patients completing the study

METABOLIC SYNDROME	NUMBER OF PARTICIPANTS	PERCENTAGE
ABSENT	13	93
PRESENT	1	7
TOTAL	14	100

Of the patients who were started on antipsychotic medications in the absence of metabolic syndrome, we were able to get complete data for 14 participants after 3 months to assess the emergence of metabolic syndrome. Out of these 14 participants, one had developed metabolic syndrome. This gives an incidence of 7%.



MetS- Metabolic Syndrome absent
MetS+ Metabolic Syndrome present

Incidence of Metabolic syndrome (NCEP ATP III criteria) at follow up (n=14)

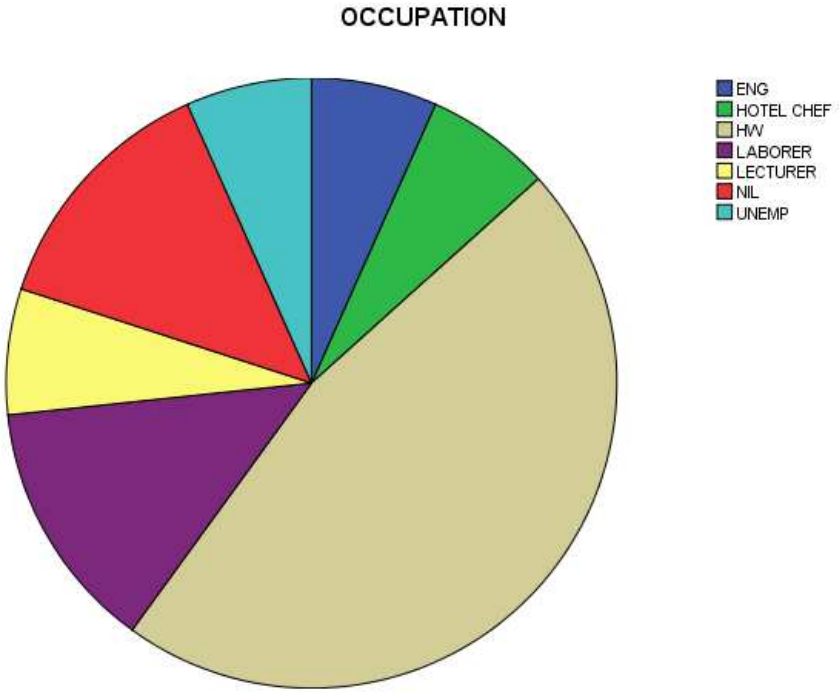
SOCIO-DEMOGRAPHIC AND TYPE OF DIET DISTRIBUTION AMONG THE PATIENTS FOLLOWED UP (WITH COMPLETE DATA)

Variable		Number of patients	Percentage	Total number of patients at follow up with complete data
GENDER	MALE	6	43	**14**
	FEMALE	8	57	
MARITAL STATUS	SINGLE	3	21	**14**
	MARRIED	11	79	
	DIVORCED/ WIDOWED	-	-	
EDUCATION	ILLITERATE	4	29	**14**
	LITERATE	10	71	
DIET	VEGETARIAN	1	7	**14**
	NON-VEGETARIAN	13	93	

Distribution according to the Occupation of patients with complete data after 3 months

OCCUPATION	NUMBER OF PARTICIPANTS	PERCENTAGE
ENGINEER	1	6.7
HOTEL CHEF	1	6.7
HOUSEWIFE	6	46.6
LABORER	2	13.3
LECTURER	1	6.7
NIL	2	13.3
UNEMPLOYED	1	6.7
Total	14	100.0

The 14 participants who were successfully followed up over 3 months had occupation status ranging from being unemployed to housewives to one lecturer. The majority comprised of housewives amounting to 47% of the followed up population.



Distribution of the antipsychotic medications prescribed among the participants followed up with complete data (n=14)

MEDICATION DETAILS	NUMBER OF PARTICIPANTS (n=14)	PERCENTAGE (%)	DOSAGE (mg)
Risperidone only	9	64	4-8
Olanzapine only#	4	29	20
Risperidone +Aripiprazole*	1	7	
Aripiprazole only	-	-	-
Other antipsychotic medication	-	-	-

#- Out of the four patients who had been treated with Olanzapine three had been on 20mg/day while one patient was on 7.5mg/day.

* One participant who had been treated with oral Risperidone (8mg/day) developed intolerable extra-pyramidal side effects within two months and was being cross tapered to Aripiprazole at the time that the review blood investigations were done. At the time of blood collections the subject had been cumulatively on Risperidone (8mg/day) for two months, Risperidone (4mg/day) for two months and Aripiprazole (20mg/day) for one month.

Out of the cohort of antipsychotic naive 14 patients with complete data, the single subject who had developed metabolic syndrome had been on Tab. Risperidone 5mg/day.

Family history of Diabetes mellitus and metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF DIABETES MELLITUS		Total
		ABSENT	PRESENT	
METABOLIC SYNROME	ABSENT	112	8	120
	PRESENT	24	4	28
Total		136	12	148

The correlation between family history of Diabetes mellitus and metabolic syndrome (NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test. This gave Pearson Chi-Square value of 1.769 with Fisher's Exact Test p value of .241. This was not statistically significant.

Family history of Hypertension and metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF HYPERTENSION		**Total**
		ABSENT	PRESENT	
METABOLIC SYNROME	ABSENT	114	6	120
	PRESENT	24	4	28
Total		138	10	148

The correlation between family history of hypertension and metabolic syndrome (NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test. This gave Pearson Chi-Square value of 3.107 with Fisher's Exact Test p value of 0.095. This was not statistically significant.

Family history of Dyslipidemia and metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF DYSLIPIDEMIA		Total
		ABSENT	PRESENT	
METABOLIC SYNROME	ABSENT	115	5	120
	PRESENT	24	4	28
Total		139	9	148

The correlation between family history of dyslipidemia and metabolic syndrome (NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test.

This gave Pearson Chi-Square value of 4.070 with Fisher's Exact Test p value of 0.066. This was not statistically significant.

Family history of Diabetes mellitus and Sub-threshold metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF DIABETES MELLITUS		Total
		ABSENT	PRESENT	
SUB-THRESHOLD METABOLIC SYNROME (at least 2 criteria of NCEP ATP III)	ABSENT	83	6	89
	PRESENT	53	6	59
Total		136	12	148

The correlation between family history of Diabetes mellitus and sub-threshold metabolic syndrome (satisfying at least 2 out of the 5 NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test. This gave Pearson Chi-Square value of 0.560 with Fisher's Exact Test p value of .543. This was not statistically significant.

Family history of Hypertension and Sub-threshold metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF HYPERTENSION		Total
		ABSENT	PRESENT	
SUB-THRESHOLD METABOLIC SYNROME (at least 2 criteria of NCEP ATP III)	ABSENT	85	4	89
	PRESENT	53	6	59
Total		138	10	148

The correlation between family history of hypertension and sub-threshold metabolic syndrome (satisfying at least 2 out of the 5 NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test. This gave Pearson Chi-Square value of 1.814 with Fisher's Exact Test p value of 0.198. This was not statistically significant.

Family history of Dyslipidemia and Sub-threshold metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF DYSLIPIDEMIA		Total
		ABSENT	PRESENT	
SUB-THRESHOLD METABOLIC SYNROME (at least 2 criteria of NCEP ATP III)	ABSENT	84	5	89
	PRESENT	55	4	59
Total		139	9	148

The correlation between family history of dyslipidemia and sub-threshold metabolic syndrome (satisfying at least 2 out of the 5 NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test.

This gave Pearson Chi-Square value of 0.084 with Fisher's Exact Test p value of 1.00. This was not statistically significant.

Family history of Diabetes mellitus and Sub-threshold metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF DIABETES MELLITUS		Total
		ABSENT	PRESENT	
SUB-THRESHOLD METABOLIC SYNROME (at least 1 criterion of NCEP ATP III)	ABSENT	35	4	39
	PRESENT	101	8	109
Total		136	12	148

The correlation between family history of Diabetes mellitus and metabolic syndrome (NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test. This gave Pearson Chi-Square value of 0.328 with Fisher's Exact Test p value of 0.516. This was not statistically significant.

Family history of Hypertension and Sub-threshold metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF HYPERTENSION		Total
		ABSENT	PRESENT	
SUB-THRESHOLD METABOLIC SYNROME (at least 1 criterion of NCEP ATP III)	ABSENT	37	2	39
	PRESENT	101	8	109
Total		138	10	148

The correlation between family history of hypertension and metabolic syndrome (NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test. This gave Pearson Chi-Square value of 0.223 with Fisher's Exact Test p value of 1.00. This was not statistically significant.

Family history of Dyslipidemia and Sub-threshold metabolic syndrome (NCEP ATP III)

		FAMILY HISTORY OF DYSLIPIDEMIA		Total
		ABSENT	PRESENT	
SUB-THRESHOLD METABOLIC SYNROME (at least 1 criterion of NCEP ATP III)	ABSENT	35	4	39
	PRESENT	104	5	109
Total		139	9	148

The correlation between family history of dyslipidemia and metabolic syndrome (NCEP-ATP III criteria) among the antipsychotic naive patients at the time of recruitment was analysed using the 2x2 Chi square test.

This gave Pearson Chi-Square value of 1.616 with Fisher's Exact Test p value of 0.244. This was not statistically significant.

INCIDENCE OF THE INDIVIDUAL COMPONENTS OF THE METABOLIC SYNDROME AFTER ANTIPSYCHOTIC USE

Incidence of increase in waist circumference

		WAIST AT FOLLOW UP	
		INCREASED	NORMAL
WAIST AT BASELINE	INCREASED	3	3
	NORMAL	11	11
Total		14	14

Among the 14 participants at follow up who had complete data, 3 had increase in their waist circumference above the norms. All three of them were female. The very same participants also had increased waist circumference at baseline. They had been recruited as they did not satisfy the diagnosis of metabolic syndrome at baseline according to the NCEP ATP III criteria. Since the very same participants continued to have increased waist circumference the incidence of increase in waist circumference in this population was zero.

Incidence of hypertension

		BLOOD PRESSURE AT FOLLOW UP	
		INCREASED (≥130/≥85 mm Hg)	NORMAL
BLOOD PRESSURE AT BASELINE	INCREASED (≥130 OR ≥85 mm Hg)	0	0
	NORMAL	14	14
Total		14	14

Among the 14 participants at follow up who had complete data, none had increase in their blood pressure above the norms. None of them had elevated blood pressure readings at the baseline. So the incidence of increase in blood pressure in this sample was zero.

Incidence of increase in fasting blood sugar levels

		FASTING BLOOD SUGAR AT FOLLOW UP	
		INCREASED (≥100 mg/dl)	NORMAL
FASTING BLOOD SUGAR AT BASELINE	INCREASED (≥100 mg/dl)	1	1
	NORMAL	13	13
Total		14	14

Among the 14 participants at follow up who had complete data, one subject had increase in the fasting blood sugar values above the norm. This was a male. He had fasting blood sugar level within normal limits at baseline. There was one female participant who had elevated blood sugar level at the time of the baseline but did not satisfy the diagnosis of metabolic syndrome at baseline according to the NCEP ATP III criteria. On follow up her fasting blood sugar level had normalised. With this information, the incidence of increase in fasting blood sugar in this sample could be considered to be 7%.

Incidence of increase in triglyceride levels

		TRIGLYCERIDE LEVELS AT FOLLOW UP	
		INCREASED (≥150 mg/dl)	NORMAL
TRIGLYCERIDE LEVELS AT BASELINE	INCREASED (≥150 mg/dl)	3	2
	NORMAL	11	12
Total		14	14

Among the 14 participants at follow up who had complete data, three subjects had triglyceride blood levels above the norm at the base line but did not satisfy the diagnosis of metabolic syndrome at baseline according to the NCEP ATP III criteria. Two out of these three individuals had normal blood levels of triglycerides at the time of follow up. One participant continued to have elevated triglyceride levels. Another subject who had normal triglyceride levels at the baseline had developed new onset hypertriglyceridemia by the follow up period. With this information, the incidence of increase in fasting blood sugar in this sample could be considered to be 7%.

Incidence of decrease in HDL cholesterol levels

		HDL CHOLESTEROL LEVELS AT FOLLOW UP	
		DECREASED (<40 mg/dl in males; <50 mg/dL in females)	NORMAL
HDL CHOLESTEROL AT BASELINE	DECREASED (<40 mg/dl in males; <50 mg/dL in females)	10	5
	NORMAL	4	9
Total		14	14

Among the 14 participants at follow up who had complete data, ten subjects had lowered HDL cholesterol blood values below the norm at the base line but did not satisfy the diagnosis of metabolic syndrome at baseline according to the NCEP ATP III criteria. These included five males and five females. Out of them five continued to have lowered HDL cholesterol levels at follow up. At the follow up the group that continued to have low levels of HDL cholesterol comprised of four males and one female. As no participants developed new onset abnormality in HDL cholesterol levels, the incidence of decrease in HDL cholesterol levels in this sample was zero.

DISCUSSION

At the start of the study we had screened 314 patients. 31 patients exercised their right not to give informed consent.

Of the remaining 283, 39 patients who had given informed consent failed to follow up in the outpatient department after the index visit. The reasons for this attrition based on the enquiry over the phone included improvement in symptoms, complete resolution of symptoms and promises of following up which were not met. Complete information could not be compiled as a number of contacts did not respond to the telephone enquiry.

Another 36 patients out of the 244 patients who gave consent, did not do the blood investigations at all.

Of the remaining 208, 60 patients could not be included due to our adherence to the requirement of doing the blood investigations within one week of the start of antipsychotic medications to cancel the effect of the medication on the metabolic profile. Blood investigations were done after the first week by 44 of the participants (being late by one day to two weeks)

16 participants had done the blood tests incompletely (12 had only done fasting blood sugars while 4 had only the lipid parameters checked). Possible reasons include two separate slips for each of these components leading to missing of one; tests being missed by the primary clinician.

Our adoption and strict adherence to, a one week criteria, seems to have contributed to a number of patients not getting recruited into the study. As most of the patients

attend psychiatric services in non-fasting state, checking of blood parameters at the index visit does not seem feasible. Other options could include provisions of providing added incentives for following up the very next day for the blood investigation or making house visits within the one week period. The cost effectiveness of such strategies will need evaluation. One of the ethical issues that has been highlighted in literature is the prevalence of “cold calling” in follow up studies(131). Cold calling refers to visiting participants at home without prior agreement. Since the purpose of home visits is for obtaining blood samples in fasting state, home visits will have to be done with prior agreement. The issues discussed above highlight the complexities involved in conducting a prospective cohort study in a clinical setting of psychiatric patients. One of the examples is the landmark BALANCE (Bipolar Affective disorder: Lithium/ANtiConvulsant Evaluation)trial where in the protocol was changed three times due to relevant clinical issues(132). This would recommend a balance between the adoption of more flexible measures to ensure good sample collection and rigid criteria to ensure qualitative standards.

Out of the total 148 subjects recruited for this study 49% were male and 52% were female. According to the population demographics data published in the Indian Census 2011, the national sex ratio is 940 females per 1000 males(133). The state of Tamil Nadu where this study was done had a higher sex ratio of 996 females per 1000 males(133). The overall trend since 2001 has been an increase in this ratio. Hence the gender distribution of the participants in our study can be considered to be reflective of the local general population.

The mean age of the patients in our study was 36 years, though the participant's age ranged from 18 years to 65 years. The majority of patients recruited in this study were suffering from psychotic illnesses, predominantly with schizophrenia. It has been well established that Schizophrenia strikes in young adults(134). This could explain the relatively younger mean age of our sample. About 66% of the subjects in our study were married, while 30% were single and the remaining 4% belonging to widowed status. According to the Indian Census 2011, in Tamil Nadu about 50.5% of the population were married with 41.9% single and remaining 7.6% in either widowed, separated or divorced status(133). The mean age at effective marriage in Tamil Nadu as of 2011 was 22.4 years(133). Given that our sample comprised of relatively younger mean age, this could explain the higher proportion of married participants in our study.

In our study sample 80% of the participants were literate. This correlates with the Indian Census 2011 figures of literacy rate of 80.3% in Tamil Nadu(133). Our sample is hence representative of the local population on this aspect as well.

Prevalence of the metabolic syndrome in antipsychotic naive mentally ill population

Out of the 148 patients recruited, abnormal HDL cholesterol levels were present in 83 subjects (44%) followed by raised triglycerides 36(24%), raised blood pressure 30 (20%), increased waist circumference 24 (16%) and impaired fasting glucose 17 (11%).

Using the criteria given by the criteria given by the NCEP ATPIII criteria 28 participants from the 147 participants recruited fulfilled the diagnosis of metabolic

syndrome. This is a prevalence rate of 19%. Most of the earlier Indian studies report prevalence rates varying from 18.3% (39) to as high as 33.5%(87). There are however differences in the diagnostic guidelines employed by these studies.

The prevalence of metabolic syndrome is lower in our study sample when compared with some previous studies (38). This can be attributed to the younger mean age as it has been shown that the prevalence of metabolic syndrome increases with increasing age.

Another factor could be the demographic and socio-economic profile of the patients using this facility. Most of the patients recruited in this study belong to the lower socio-economic strata, while studies in India have shown positive correlation between metabolic syndrome and middle to high socio-economic status(87). Previous Indian study samples merged data of truly antipsychotic naive patients with those who had been off the antipsychotic medication for a specified duration of time(54,103). In our study we strictly adhered to the inclusion of only those patients who had never been exposed to antipsychotic medication. Therefore the data collected from this sample of patients would represent the incidence of deranged metabolic status in truly antipsychotic naive population where in carry over effects of previous antipsychotic medication use is absent.

Another difficulty in comparison with other Indian research, is that many studies did not recruit antipsychotic naive participants(98,102,135). Previous Indian research varies in the duration for which participants were on antipsychotic medications, ranging from short durations of 6 weeks (57) and 8 weeks (99) to one year duration(95)

Using the IDF criteria, the prevalence rate in this study is 12%. Previous Indian studies report prevalence rates using the IDF criteria from as low as 10.86% (101) to as high as 18.2% (104) in patients with schizophrenia. Hence the prevalence rate in this study using the IDF criteria is comparable to findings from other parts of India. The comparative lower prevalence rate when using the IDF criteria could be attributed to its more restrictive pattern of diagnosis which requires the presence of central obesity as a prerequisite.

The gender specific prevalence of metabolic syndrome in our sample, calculated according to the NCEP ATP III guidelines gives a comparable prevalence rates among the genders (female 16% and male 17%).This is in keeping with earlier international studies which have shown an equal prevalence of metabolic syndrome in males and females(136). On the other hand some Indian studies have shown higher prevalence among females(38,86).

Substance use and the metabolic syndrome

About 18% of the patients in our study had concomitant use of tobacco. Though the earlier concept was that tobacco has protective effects on central obesity(56,96), it has been established that tobacco has positive correlation with metabolic syndrome(137–139). Analysis of association between tobacco use and the prevalence of metabolic syndrome using Chi square comparison did not yield any statistically significant results.

Of the total 148 patients 14% also used alcohol, though not amounting to dependence pattern. Heavy alcohol use has been associated with metabolic syndrome(140).

Statistical analysis did not however reveal any significant association between alcohol use and the prevalence of metabolic syndrome in the population recruited.

With the current data from this study we cannot demonstrate a relationship between substance use and metabolic syndrome.

Family history as a risk factor

In our study sample family history of dyslipidemia, hypertension and diabetes mellitus was present in 6%, 7% and 8% respectively. Analysis of the association between these family histories and the prevalent metabolic syndrome in the recruited population did not show any statistically significant results.

We also analysed the correlation between family history and presence of sub-threshold metabolic syndrome, however statistically significant association was not found. Literature review also showed limited information for the correlation between family history and metabolic syndrome except for some studies on the positive correlation with family history of cardiovascular disease(141) and diabetes mellitus(142). Though a positive correlation seems plausible theoretically, the data from the current study does not support this.

Diet and the metabolic syndrome

Based on the diet patterns, 87 % of the patients in our study were on non-vegetarian diet. Our analysis did not yield any statistically significant associations between the type of diet and metabolic syndrome. There is inconclusive evidence in the literature about the protective effects of vegetarian diet on metabolic syndrome(143,144). This would also be governed by genetic variations in different ethnicities.

Prevalence of at least two and at least one component of metabolic syndrome

In our baseline sample 40% participants satisfied at least two components of the metabolic syndrome. In comparison about 74% subjects satisfied at least one component of the metabolic syndrome criteria as defined by NCEP ATP III. Recently, pooled data from three Indian studies on patients with schizophrenia showed that when antipsychotic naive patients were checked for the sub-threshold metabolic syndrome defined by criteria of satisfying either at least two or at least one out of the 5 components, the prevalence rates were 23.3% and 40.9% respectively(96).

The prevalence of the individual components of the metabolic syndrome in antipsychotic naive patients in our study is much higher. This is a finding that requires further study.

This also highlights the need for further research on antipsychotic naive patients to identify sub-threshold metabolic syndrome and the risk factors that can be targeted in prevention strategies against progression to full blown metabolic syndrome.

Distribution of individual components of metabolic syndrome

Among the 28 antipsychotic naive patients who were diagnosed to have metabolic syndrome at the outset using the NCEP ATP III criteria, 78.57% had abnormal HDL cholesterol levels, followed by 71.43% with elevated fasting blood sugar levels and 60.72% with increased waist circumferences. 60.71% participants had both hypertriglyceridemia and hypertension. So this means that maximum number of patients had abnormal HDL cholesterol levels followed by waist circumference & elevated fasting blood sugar levels. This is different from one study which found

blood pressure, HDL cholesterol and triglycerides to be the most common components contributing to the metabolic syndrome(86).

As the number of patients with complete data on follow up was small, factor analysis between the individual components of the metabolic syndrome and antipsychotic medication use could not be done.

One component which has been found to be among the most common contributors to metabolic syndrome in Indian studies has been increased waist circumference(38,83,84). This difference may be due to the ethnic and genetic propensity for Indians to develop central obesity. This would suggest that diagnostic criteria using waist circumference as one of the major components might be of more relevance to the Indian population. This trend is not seen in this study.

Incidence of metabolic syndrome

Out of the 147 patients recruited for this study only 14 patients could be followed up after 3 months for assessment of metabolic syndrome. This accounts for 10% of the sample recruited. Of this 10%, participants belonging to the female gender comprised of 47%. The rate of literacy did not markedly differ between the baseline population and the follow up population. Since the attrition rate was as large as 90%, the incidence rates and the risk factor variables could not be statistically analysed any further.

89 patients did not come for follow up visits to the outpatient department. Attempts were made to ensure adherence with therapy by calling up individual patient on their mobile phones. A number of participants responded to the phone calls with promises of following up in the outpatient clinics which did not materialize. Reasons given over

the phone for not coming for the review appointments included improvement in symptoms and in some cases complete resolution of symptoms. Complete information could not be compiled as many contacts did not respond to the telephone enquiry.

8 patients attended the outpatient department, but did not come in a fasting state for the blood measurements, and therefore, could not provide the required data. Measuring the blood parameters at the patient's local medical laboratory was considered but decided against, due to the lack of standardization of quality of analysis.

The incidence of metabolic syndrome using the NCEP ATP III criteria among the patients followed up is 7%. This corresponds with incidence rate of 11% reported by another recent study from northern part of India (103). In this small sample among the individual components of the metabolic syndrome only parameters with new onset abnormalities were in fasting blood sugar and triglyceride levels. This increase was by one case in each parameter. Inferences cannot be made on this finding. Due the small sample of the follow up the correlation between the defined variables and the incidence of metabolic syndrome could not be analysed. As none of the followed up participants had increased waist circumference, incidence was zero using the IDF criteria.

Antipsychotic medication and the incidence of metabolic syndrome

In our study sample, majority of the patients had been on the atypical antipsychotic medication Risperidone, followed by Olanzapine. According to international studies, Risperidone is associated with relatively lesser propensity to develop metabolic syndrome in comparison to Olanzapine(61,62,66). Though these studies were done

predominantly in American and European populations, recent literature review has shown that the risks associated with use of atypical antipsychotic medications are comparable in East Asian and other populations(146).

In this study the single individual who developed metabolic syndrome among the 14 participants (with complete data) was on Risperidone. The lack of adequate sample size impedes any statistical interpretation of these findings. However clinically it would be advisable for clinicians to consider and guard against metabolic syndrome even when antipsychotic medications of lesser risk profile like Risperidone are prescribed.

Strengths of the study

1. This study examined an area that is of clinical significance and for which there is sparse national or regional information.

2. In this study consecutive patients attending the tertiary care psychiatric services in Southern India were recruited. This limited selection bias.

3. The sample included only antipsychotic naive patients which are in contrast to numerous previous studies which have merged data from purely antipsychotic naive and those off antipsychotic medications for stipulated periods of time, and therefore measured true incidence.

4. Data regarding risk factors like family history had been compiled which has been missed out in previous studies.

Limitations of the study

1. The baseline sample size could not be reached.

2. The dropout rate was very high.

3. Adherence to a strict protocol resulted in further attrition of data.

4. Although most of the results replicate findings from previous studies, the results are marred by lack of statistical significance

5. Due to the large loss to follow up, all planned statistical calculations could not be done.

Clinical Implications

This study has found that the prevalence of metabolic syndrome in patients with mental illness attending the services of this tertiary care psychiatric centre in South India is high even before the start of antipsychotic therapy. The presence of sub threshold metabolic syndrome is also very high.

This study also highlights the high rate of drop out among patients with psychiatric illness, in spite of active measures to ensure good adherence to therapy.

Clinicians need to be aware of the implications regarding the prescription of psychiatric medications and the preventive measures that need to be adopted against the development of metabolic syndrome.

Baseline recording of anthropometric data and the laboratory parameters is essential before starting antipsychotic medications. This would enable the identification of vulnerable patients and inform clinical practice on the choice of antipsychotic medication.

This study also shows that clinicians need to remain vigilant while prescribing antipsychotic medications with relatively lesser risk of metabolic syndrome.

In addition this study also highlights the importance of having monitoring schedules in place to ensure that the development of any new features of metabolic syndrome among patients on antipsychotic medications is not missed. This should comprise of regular physical measurements and laboratory investigations.

Future directions

Prospective studies using a cohort design of antipsychotic naive patients with a control group should provide accurate data on the incidence of metabolic syndrome. The choice of a suitable control group where antipsychotic medication will not be administered raises several ethical issues and requires careful planning.

Studies with large sample sizes and good follow up rates will inform clinical practice. High dropout rates are a clinical reality. Hence, improving follow up rates and data collection is a challenge. Strategies possible include offering incentives for remaining in follow up, using local laboratory facilities for tests, and home visits with consent for this to be included at the start of the study. These raise ethical, financial, and quality control issues during the planning.

This study has demonstrated that a large proportion of patients with mental illness already have deranged metabolic functions, with a significant subset qualifying for the diagnosis of metabolic syndrome even prior to the institution of antipsychotic medication therapy. This highlights the need for further studies to explore the relationship between metabolic syndrome and mental illness. Further research needs to focus on the factors contributing to this increased prevalence.

Nearly 75% of the sample had at least one deranged metabolic parameter before treatment. This underlines the need for further exploration of sub-threshold metabolic syndrome, and the appropriateness of the cut offs to qualify for a diagnosis of the full syndrome.

Another finding from this study is the high rates of drop out to tertiary psychiatric care service. This opens up another avenue for research into factors affecting adherence with mental health care.

Finally this study has replicated similar incidence rates for antipsychotic drug emergent metabolic syndrome as in other Indian studies. Indian psychiatrists must enforce screening, primary prevention, and early detection and treatment of this syndrome.

SUMMARY

Introduction

Metabolic syndrome constitutes a constellation of risk factors which predispose individuals toward the development of diabetes mellitus and coronary artery disease. Studies have demonstrated association between metabolic syndrome and mentally ill patients. With the current shift in psychopharmacological prescription patterns and the increased use of second generation antipsychotics, the significance of metabolic syndrome in psychiatric populations has increased. Other contributing factors in the mentally ill patients towards development of metabolic syndrome are sedentary life style and diet.

Extensive literature review revealed a dearth of data on both the prevalence of metabolic syndrome and the incidence of metabolic syndrome among Indian populations with mental illness.

Methodology

A prospective cohort study was conducted where the prevalence of metabolic syndrome in antipsychotic naive patients was measured at the time of recruitment. Those who did not fulfil the criteria for metabolic syndrome and required antipsychotic medications were followed up over a period of 3 months and reassessed for the incidence of metabolic syndrome. Participants fulfilling the inclusion and exclusion criteria were recruited from both outpatient and inpatient facilities in the department of Psychiatry, Christian Medical College, Vellore. This was done after obtaining written informed consent. Socio-demographic, anthropometric, blood pressure and blood parameters (HDL cholesterol, triglycerides, and fasting blood sugars) were recorded in addition to making note of other risk factors such as family history.

Results

The analysis of the baseline characteristics was done using 148 participants. The prevalence of metabolic syndrome in antipsychotic naive patients with mental illness was 19% using the NCEP ATP III definition while it was 12% when using the IDF criteria. The prevalence of sub threshold metabolic syndrome was 40% when only 2 criteria and 74% when any one of the NCEP ATP III criteria were fulfilled.

Full data was available for 14 participants three months later. In this sub group the incidence rate for metabolic syndrome was 7% using the NCEP ATP III definition.

Conclusion

The prevalence of metabolic syndrome in drug naïve patients was found to be comparable to other Indian studies. The prevalence of sub-threshold metabolic syndrome was much higher than previously reported.

There was a high dropout rate.

The incidence rate of metabolic syndrome was comparable to one earlier Indian study.

There is need for further studies to identify the clear incidence and risk factors of metabolic syndrome with antipsychotic use.

This study also highlights the need for clinicians to be thoughtful about choosing antipsychotic medications, to document relevant clinical parameters before starting therapy, to be aware of the risks of precipitating metabolic syndrome in vulnerable populations and to adopt necessary strategies to prevent the emergence of this syndrome.

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APPENDIX 1

Participant Information Sheet

"Incidence of metabolic syndrome in patients receiving antipsychotic medication"

My name is Dr. Akhil Abhijnhan and I am doing a research on a condition called metabolic syndrome. The research will be done in Department of Psychiatry, CMC, Vellore.

Medications can cause various side effects and antipsychotic drugs which you are receiving may result weight gain, rise in blood sugar, blood pressure and cholesterol.

I am aiming to find out these by checking your waist circumference and testing your blood. I would like to request you to donate 10 ml (2 teaspoonfuls) of blood during my study. Your blood and waist circumference will be checked twice: once at the time that you are enrolled into this study and a second time after 3 months. I will also be collecting information regarding your illness from the case record kept in the hospital.

The blood will be taken using sterile (clean) methods by a trained technician. Your information will not be revealed to anyone and all information about you and your treatment will be kept confidential. The blood tests will be done free of cost and the bus fare for coming to hospital for doing blood tests will be reimbursed for local patients. This study is not likely to be of any direct benefit to you.

You have every right to refuse to take part in this study. Your treatment will not be affected by this.

If you have any doubts you can contact me at 04162284520, department of Psychiatry, CMC, Vellore. Email: akhil.abith@gmail.com.

APPENDIX 2

Consent Form

"Incidence of metabolic syndrome in patients receiving antipsychotic medication"

I.....residing in.....

..... give consent to take part in a study that looks at presence of raised blood sugars, cholesterol, blood pressure and weight in patients receiving antipsychotic medication. The research has been explained to me in the language known to me. I was given the chance to ask questions about the study. I have received an information sheet as well in my regional language.

My treatment will be the same whether I take part in the study or not. There is no direct benefit to me because of this study. I will not receive any money or gift for taking part in the study other than the travel expenses. My personal details will not be disclosed to anyone .I have no objection for the study results being published in a scientific journal .I can withdraw from the study at any point of this research.

Signature of the participant/Thumb impression: Date

Signature of the researcher: Date

Relative's Consent Form

I..... being the..... of ..... hereby confirm that I have been explained about the study titled "Incidence of metabolic syndrome in patients receiving antipsychotic medication". I have been explained in detail about the purpose and procedures involved in this study.

..... hereby give consent on behalf of the patient for this study.

Signature of the relative/Thumb impression: Date

Relation to the patient:

Signature of the researcher: Date

APPENDIX 3

நோயாளிகளின் தகவல் படிவம்

ஆன்டிசைகாட்டிக் மருந்து எடுக்கும் நோயாளிகளுக்கு ஜிரண கோளாறுகளால் ஏற்படும் விளைவுகள்

ஆய்வின் தலைப்பு:
என் பெயர் டாக்டர். அக்கில், நான் ஆன்டிசைகாட்டிக் மருந்து எடுக்கும் நோயாளிகளுக்கு ஜிரண கோளாறுகளால் ஏற்படும் விளைவுகள்பற்றி ஒரு ஆராச்சி செய்கிறேன்.

ஆராச்சி நிலையம்:
மனநல மருத்துவமணை, கிருஸ்த்துவ மருத்துவக் கல்லூரி, பாகாயம் , வேலூர்.

ஆய்வின் நோக்கம்:
மருந்து பக்கவிளைவுகளை ஏற்படுத்தும் நிங்கள் எடுத்துக்கொண்டுடிருக்கும் ஆன்டிசைகோடிக் மருந்து உடல் எடை கூடுதலை , சர்க்கரை நோய் , இரத்த கொதிப்பு, இரத்த கொழுப்பு, போன்ற பக்கவிளைவுகளை ஏற்படுத்தும் வாய்ப்பு உள்ளது. எனவே இந்த பக்கவிளைவுகள் உங்களுக்கு ஏற்பட்டுள்ளதா என்று சரிபார்க்க இரத்த பரிசோதனை செய்யப்படும்.

பின்பற்ற இருக்கும் செயல்முறை:
இந்த ஆய்விற்காக 10 m.l. இரத்து கொடுக்க உங்களை கேட்டுக்கொள்ளுகிறோம் மற்றும் உடல் எடை கூடுதலை சரிபார்க்க உங்கள் இடுப்பின் அளவேடுக்கபடும் தற்போழுது ஒருமுறையும் மறுபடியும் மூன்று மாதத்திற்கு பிறகு ஒருமுறை அளவெடுக்கபடும்.

இந்த ஆய்வின் மூலம் ஏற்படும் நன்மைகள்:
உங்களுடை நோய் குறித்தான விவரங்களை கேட்டு சேகரிக்கப்படும். இரத்த பரிசோதனை இலவசமாக செய்யப்படும் மற்றும் போக்குவறத்து பேருந்து செலவு கொடுக்கப்படும். இந்த ஆராச்சியில் பங்குக்கொள்வதினால் உங்களுக்கு எந்தவொறு நேரடி பயன் இருக்காது.

இரகசியக்காப்பு:

இந்த ஆய்வின் ஆவனங்கள் மற்றும் இந்த ஆய்வில் பெறப்படும் தகவல்கள் அனைத்தும் மிகவும் இரகசியமாக வைக்கப்படும். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவரை தவிர மற்றவர்களுக்கு எப்பொழுதும் தெரியப்படமாட்டது. தங்களின் தனிப்பட்ட தகவல்கள் இந்த ஆய்விற்காக மட்டுமே பயன்படுத்தப்படும். தங்களின் பெயர் மற்றும் அடையாளம் எந்தவித வெளியீட்டிலும் தெரியபடுத்தமாட்டாது.

ஆய்விலிருந்து விலகிக்கொள்வதற்கான உரிமை:

இந்த ஆய்விலிருந்து விலகிக்கொள்வதற்கு எந்த நேரமும் தங்களுக்கு முழு சுதந்திரம் உண்டு. தாங்கள் இந்த ஆய்வில் பங்கேற்பதற்கும் அல்லது மறுப்பு தெரிவிப்பதற்கும் எடுக்கும் முடிவு இந்த மருத்துவமனையில் மேற்கொண்டு தொடர்ந்து மருத்துவ அல்லது மனநோய் சிகிச்சை பெறுவதை எந்த வகையிலும் பாதிக்காது. மேலும் சந்தேகங்களுக்கு கீழ்கண்ட முகவரியினை தொடர்புகொள்ளுங்கள்.

டாக்டர் : அக்கில்
மனநல மருத்துவப்பிரிவு
கிருஸ்த்துவ மருத்துவக் கல்லூரி
வேலூர் - 632 002.

தொலைப்பேசி எண்: 0416 - 2284520 [8056342227]
இபெயில் : psych2@cmcvellore.ac.in
akhil.abith@gmail.com

APPENDIX 4

ஒப்புதல்

திரு / திருமதி ..... என்கின்ற எனக்கு ஆன்டிசைகாட்டிக் மருந்து எடுப்பதால் ஜிரண கோளாறுகளால் ஏற்படும் விளைவுகளைப் பற்றிய ஆய்வினை எனக்கு தகவல்கள் தெரிவிக்கப்பட்டது. இந்த ஆய்வின் விவரங்கள் பற்றி ஆய்வாளர் எனக்கு தெளிவாக எடுத்துக் கூறினார். நான் என் சொந்த விருப்பத்தில் இந்த ஆய்வில் கலந்துக்கொள்வதற்கு சம்மதம் தெரிவித்துக் கொள்கிறேன்.

கலந்துகொள்பவரின் கையொப்பம் : தேதி

ஆய்வாளரின் கையொப்பம் : தேதி

உறவினரின் ஒப்புதல்

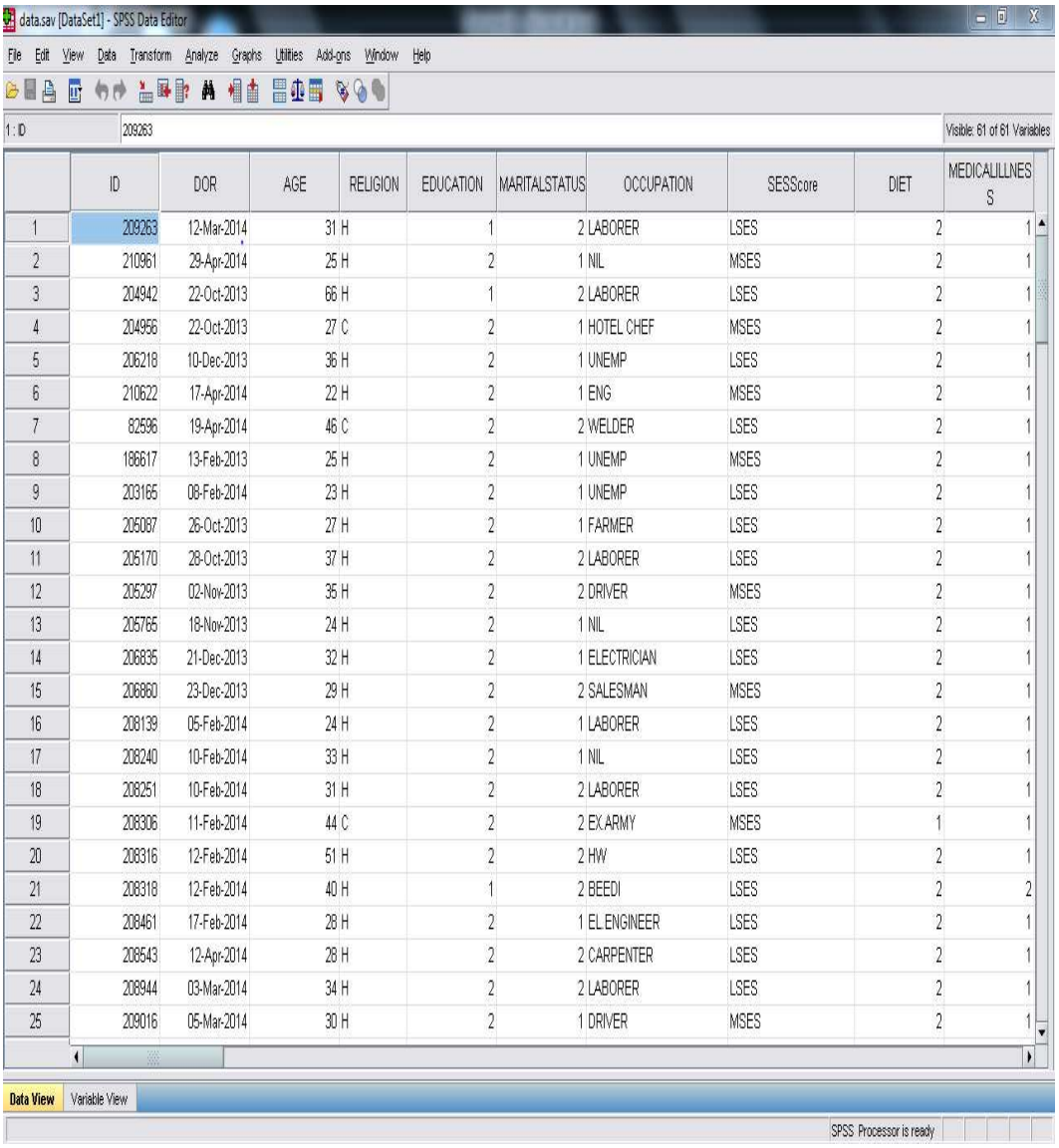
..... என்பவரின் .....ஆகிய ..... என்கின்ற எனக்கு ஆன்டிசைகோடிக் மருந்து எடுப்பதால் ஜிரண கோளாறுகளால் ஏற்படும் விளைவுகளைப் பற்றிய ஆய்வினை எனக்கு தகவல்கள் தெரிவிக்கப்பட்டது. இந்த ஆய்வின் விவரங்கள் பற்றி ஆய்வாளர் எனக்கு தெளிவாக எடுத்துக் கூறினர். ..... இந்த ஆய்வில் கலந்துக்கொள்வதற்கு அவரது சார்பாக நான் சம்மதம் தெரிவித்துக் கொள்கிறேன்.

உறவினரின் கையொப்பம் : தேதி

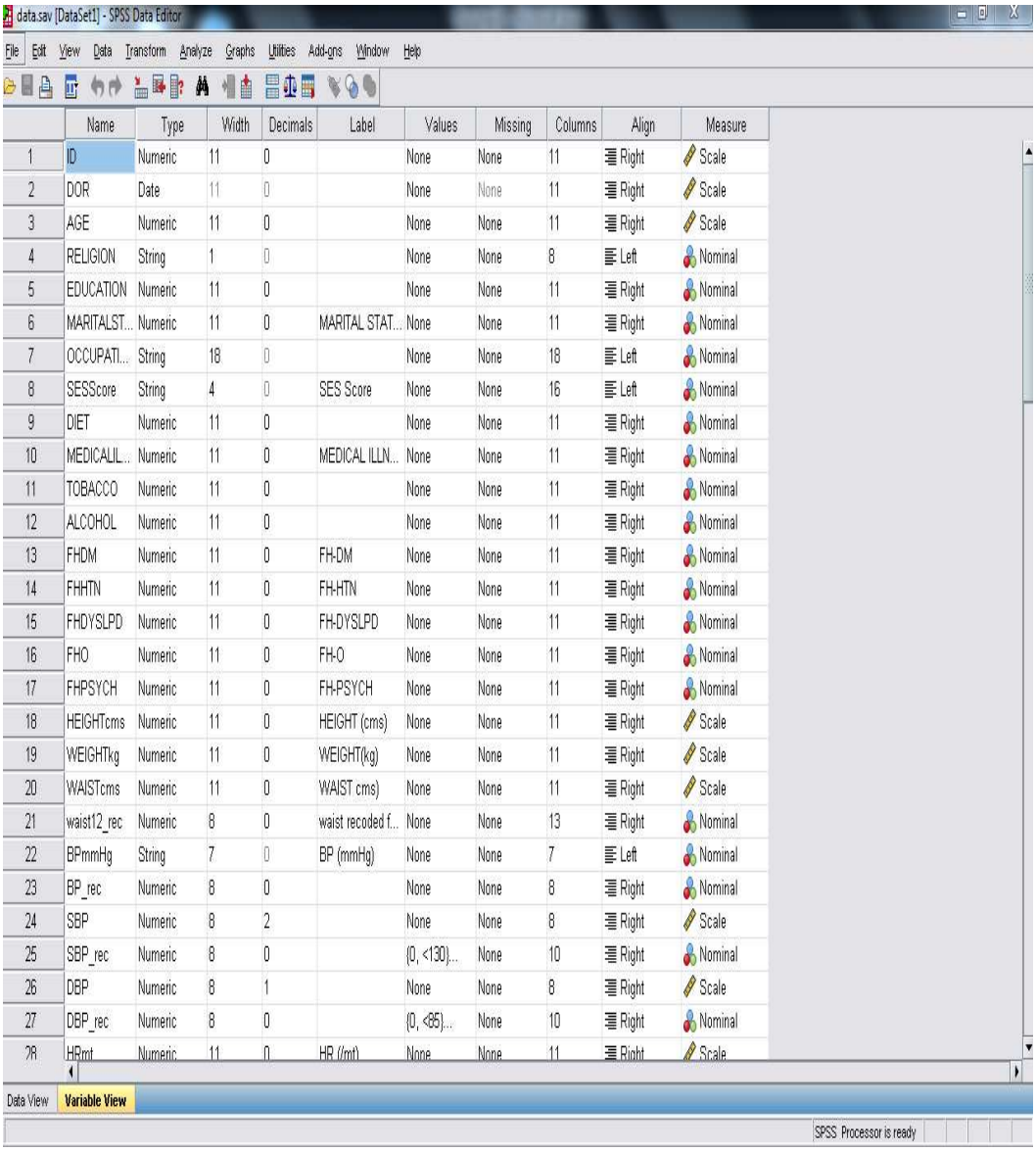
உறவுமுறையின் பெயர் :

ஆய்வாளரின் கையொப்பம் : தேதி

SPSS



	ID	DOR	AGE	RELIGION	EDUCATION	MARITALSTATUS	OCCUPATION	SESScore	DIET	MEDICALILLNESS
1	209263	12-Mar-2014	31	H	1	2	LABORER	LSES	2	1
2	210961	29-Apr-2014	25	H	2	1	NIL	MSES	2	1
3	204942	22-Oct-2013	66	H	1	2	LABORER	LSES	2	1
4	204956	22-Oct-2013	27	C	2	1	HOTEL CHEF	MSES	2	1
5	206218	10-Dec-2013	36	H	2	1	UNEMP	LSES	2	1
6	210622	17-Apr-2014	22	H	2	1	ENG	MSES	2	1
7	82596	19-Apr-2014	46	C	2	2	WELDER	LSES	2	1
8	186617	13-Feb-2013	25	H	2	1	UNEMP	MSES	2	1
9	203165	08-Feb-2014	23	H	2	1	UNEMP	LSES	2	1
10	205087	26-Oct-2013	27	H	2	1	FARMER	LSES	2	1
11	205170	28-Oct-2013	37	H	2	2	LABORER	LSES	2	1
12	205297	02-Nov-2013	35	H	2	2	DRIVER	MSES	2	1
13	205765	18-Nov-2013	24	H	2	1	NIL	LSES	2	1
14	206835	21-Dec-2013	32	H	2	1	ELECTRICIAN	LSES	2	1
15	206860	23-Dec-2013	29	H	2	2	SALESMAN	MSES	2	1
16	208139	05-Feb-2014	24	H	2	1	LABORER	LSES	2	1
17	208240	10-Feb-2014	33	H	2	1	NIL	LSES	2	1
18	208251	10-Feb-2014	31	H	2	2	LABORER	LSES	2	1
19	208306	11-Feb-2014	44	C	2	2	EX ARMY	MSES	1	1
20	208316	12-Feb-2014	51	H	2	2	HW	LSES	2	1
21	208318	12-Feb-2014	40	H	1	2	BEEDI	LSES	2	2
22	208461	17-Feb-2014	28	H	2	1	EL ENGINEER	LSES	2	1
23	208543	12-Apr-2014	28	H	2	2	CARPENTER	LSES	2	1
24	208944	03-Mar-2014	34	H	2	2	LABORER	LSES	2	1
25	209016	05-Mar-2014	30	H	2	1	DRIVER	MSES	2	1



	Name	Type	Width	Decimals	Label	Values	Missing	Columns	Align	Measure
1	ID	Numeric	11	0		None	None	11	Right	Scale
2	DOR	Date	11	0		None	None	11	Right	Scale
3	AGE	Numeric	11	0		None	None	11	Right	Scale
4	RELIGION	String	1	0		None	None	8	Left	Nominal
5	EDUCATION	Numeric	11	0		None	None	11	Right	Nominal
6	MARITALST...	Numeric	11	0	MARITAL STAT...	None	None	11	Right	Nominal
7	OCCUPATI...	String	18	0		None	None	18	Left	Nominal
8	SESScore	String	4	0	SES Score	None	None	16	Left	Nominal
9	DIET	Numeric	11	0		None	None	11	Right	Nominal
10	MEDICALIL...	Numeric	11	0	MEDICAL ILLN...	None	None	11	Right	Nominal
11	TOBACCO	Numeric	11	0		None	None	11	Right	Nominal
12	ALCOHOL	Numeric	11	0		None	None	11	Right	Nominal
13	FHDM	Numeric	11	0	FH-DM	None	None	11	Right	Nominal
14	FHHTN	Numeric	11	0	FH-HTN	None	None	11	Right	Nominal
15	FHDYSLPD	Numeric	11	0	FH-DYSLPD	None	None	11	Right	Nominal
16	FHO	Numeric	11	0	FH-O	None	None	11	Right	Nominal
17	FHPSYCH	Numeric	11	0	FH-PSYCH	None	None	11	Right	Nominal
18	HEIGHTcms	Numeric	11	0	HEIGHT (cms)	None	None	11	Right	Scale
19	WEIGHTkg	Numeric	11	0	WEIGHT(kg)	None	None	11	Right	Scale
20	WAISTcms	Numeric	11	0	WAIST cms)	None	None	11	Right	Scale
21	waist12_rec	Numeric	8	0	waist recoded f...	None	None	13	Right	Nominal
22	BPmmHg	String	7	0	BP (mmHg)	None	None	7	Left	Nominal
23	BP_rec	Numeric	8	0		None	None	8	Right	Nominal
24	SBP	Numeric	8	2		None	None	8	Right	Scale
25	SBP_rec	Numeric	8	0		{0, <130}...	None	10	Right	Nominal
26	DBP	Numeric	8	1		None	None	8	Right	Scale
27	DBP_rec	Numeric	8	0		{0, <85}...	None	10	Right	Nominal
28	HRmt	Numeric	11	0	HR (/mt)	None	None	11	Right	Scale